

doi: 10.30827/ars.v64i3.27249

Artículos originales

Pharmaceutical interventions and factors associated with their acceptance in intensive care units in Brazil

Intervenciones farmacéuticas y factores asociados a su aceptación en unidades de cuidados intensivos en Brasil

Ana Vitória Martins de Oliveira¹  0000-0002-9413-4717

Elana Figueiredo Chaves¹  0000-0002-5817-0999

Amanda Mota Conceição¹  0000-0002-4638-8130

Liana Moreira Magalhães¹  0000-0002-2950-8540

Breno Queiroz de Araújo¹  0000-0002-6354-5660

Cinthya Cavalcante de Andrade²  0000-0001-5812-7213

José Martins de Alcântara Neto²  0000-0002-6354-6006

Alene Barros de Oliveira²  0000-0002-4767-2256

¹Federal University of Ceará, Walter Cantídio University Hospital, Multiprofessional Integrated Residency Program in Hospital Health Care, Fortaleza, Brazil.

²Federal University of Ceará, Walter Cantídio University Hospital, hospital pharmacy service, Fortaleza, Brazil.

Correspondence

Surname: Martins de Oliveira Name: Ana Vitória
anavitoriamoliveira@gmail.com

Received: 26.01.2023

Accepted: 30.03.2023

Published: 20.06.2023

Acknowledgment

The authors are grateful for the contribution of the physicians, pharmacists and patients of the Walter Cantídio University Hospital who collaborated in the conduction of this study.

Funding

The research did not receive funding for its realization.

Conflict of interest

The authors declare that there are no conflicts of interest in relation to this article.

Resumen

Objetivo: El propósito de este estudio es evaluar las intervenciones farmacéuticas (IF) realizadas sobre PRM y los factores asociados a su aceptación.

Método: Se trata de un estudio descriptivo y transversal que analizó las IF realizadas a pacientes adultos de dos UCI de Fortaleza, Brasil, en 2019. Las IF se analizaron en las categorías cantidad de fármaco y estrategia farmacológica, utilizando la clasificación propuesta por Sabater *et al.* Los fármacos se clasificaron además por el Sistema de Clasificación Anatómica, Terapéutica, Química y por la clasificación de Fármacos de Alta Vigilancia (FAV).

Resultados: Se incluyeron 305 pacientes, siendo la mayoría del sexo masculino (55,1 %), ancianos (52,8 %) y atendidos en la UCI quirúrgica (51,4 %). Se analizaron 1.317 IF y se aceptaron el 88,0 %, siendo la sustitución de uno o más fármacos (28,0 %) y la adición de uno o más fármacos (27,7 %) las más frecuentes. La clase terapéutica más prevalente fue antiinfeccioso de uso sistémico (24,1 %) y los FAV estuvieron implicados en el 21,7 % de las IF. Se observó asociación entre las IF aceptadas e ingreso en UCI clínica ($p < 0,0001$), FAV ($p = 0,0013$), sustitución de uno o más fármacos ($p = 0,0062$) y la clase sustitutos sanguíneos y soluciones de perfusión ($p = 0,0187$).

Conclusiones: Se realizaron y aceptaron un elevado número de IF, lo que refuerza la importancia del farmacéutico en la revisión de las prescripciones médicas en UCI.

Palabras clave: Farmacoterapia; Servicios Farmacéuticos; Unidades de Cuidados Intensivos

Abstract

Objective: The purpose of this study is to evaluate the pharmaceutical interventions (PI) performed in PRM and the factors associated with their acceptance.

Method: This is a descriptive and cross-sectional study that analyzed PIs performed on adult patients from two ICUs in Fortaleza, Brazil, in 2019. PIs were analyzed in the categories quantity of drug and pharmacological strategy, using the classification proposed by Sabater *et al.* The drugs were also classified by the Anatomical, Therapeutic, and Chemical Classification System and by the High Surveillance Drugs (FAV) classification.

Results: 305 patients were included, most of them male (55.1 %), elderly (52.8 %) and treated in the surgical ICU (51.4 %). 1,317 PIs were analyzed and 88.0 % were accepted, being to replace one or more drugs (28.0 %), to add one or more drugs (27.7 %) and to change the dose (24.8 %) the most frequent types. The most prevalent therapeutic class was anti-infectives for systemic use (24.1 %) and AVFs were involved in 21.7 % of the PIs. An association was observed between PIs accepted and admission to the clinical ICU ($p < 0.0001$), AVF ($p = 0.0013$), substitution of one or more drugs ($p = 0.0062$) and the class of blood substitutes and perfusion solutions. ($p = 0.0187$).

Conclusions: A high number of PIs were performed and accepted, which reinforces the importance of the pharmacist in the review of medical prescriptions in the ICU.

Keywords: Drug Therapy; Pharmaceutical Care; Intensive Care Units

Highlights

The clinical pharmacist is recognized as an essential member of the multiprofessional care team in ICU. Their performance is associated with better clinical outcomes. In Brazil, studies about pharmaceutical interventions (PI) are scarce and do not present a standard on how to classify PIs, which makes it difficult to compare the results.

This article shows the PIs carried out in two ICUs of a university hospital, using the classification proposed by Sabater *et al.*, as well as investigating the possible factors associated with this acceptability.

A real association is established between the accepted PIs and with 1) admissions to the clinical ICU, 2) prescriptions for high-vigilance medications, 3) substitution interventions for one or more medications, and 4) therapeutic class therapeutic class blood substitutes and perfusion solutions.

Introduction

The pharmacotherapy of patients in Intensive Care Units (ICU) is complex and represents a major risk factor for the occurrence of drug-related problems and adverse events.^(1,2) Patients with severe clinical status and multiple drugs' use - often as off-label or considered potentially dangerous - complicate the

management of pharmacological therapies, which reinforces the importance of intensive care pharmacists for monitoring these patients.⁽³⁾

The intensive care pharmacists are recognized by the Society of Critical Care Medicine (SCCM) as an essential members of the multidisciplinary ICU care team, and their role is also covered by current Brazilian legislation.⁽⁴⁻⁵⁾ The impact of their participation in the intensive care team has been increasingly studied in the past years and has been associated with better clinical outcomes, reduced mortality and length of hospital stay, better infection control, promotion of adequate use of protocols for gastric ulcer prophylaxis and ICU sedation, decreased incidence of drug side effects and reduction of drug costs.⁽⁶⁻⁹⁾

The activities of intensive care pharmacists in the daily care of patients in ICUs include participation in daily clinical visits, analysis of the prescribed pharmacotherapy, drug reconciliation, identification, and prevention of drug adverse reactions and, whenever appropriate, proposal of pharmaceutical interventions (PI).^(10,11) PIs are defined as the professional, planned and documented action performed by a pharmacist, with the purpose of optimizing pharmacotherapies and promoting health.⁽¹²⁾

According to Shulman *et al.* (2015), in a study carried out in the United Kingdom, about one in six drug prescriptions in ICUs require PIs, with two-thirds of them being classified as of having moderate to high impact.⁽¹³⁾ In another study conducted in the United States of America, the presence of the pharmacist at clinical visits reduced adverse event rates by 66 % when 99 % of pharmaceutical therapy management interventions were accepted, and this had an estimated cost reduction of 270 thousand dollars a year.⁽¹⁴⁾

Despite there are several studies worldwide on the role of clinical pharmacists in ICUs, studies in Brazil are still scarce and do not present standardization on how to classify PIs, which hampers proper comparison of findings. Therefore, this study aimed to evaluate PIs performed in two ICUs of a university hospital, using the classification proposed by Sabater *et al.*⁽¹⁵⁾, and assess possible factors associated with their acceptance.

Methods

This was a descriptive and cross-sectional study, with a quantitative approach, which analyzed PIs directed to the multidisciplinary team in clinical and surgical ICUs of a university hospital in Fortaleza, Brazil, from January to December 2019. The study was carried out with the approval of the Research Ethics Committee of the institution, with exemption from the application of the Free and Informed Consent Form, number 2,084,853 and CAEE: 74283417.4.0000.5045.

The study site is integrated into the Unified Health System (SUS) of Brazil and offers high-complexity health care. The ICUs studied have eight active beds each for the care of adult patients, one for surgical patients, and have a multidisciplinary team structured of physicians, nurses, nursing technicians, physiotherapists, pharmacists, and nutritionists, as well as resident professionals from each area. The team of clinical pharmacists in the ICU is composed of seven pharmacists, of which one is an intensive care staff and six are resident pharmacists in intensive care. In each ICU, at least two resident pharmacists work under supervision of staff, with an average of 5 hours of care per day on weekdays.

The organization of pharmaceutical care was based on 1) review of the patient's chart with cranio-caudal assessment of clinical and laboratory parameters, 2) technical analysis of the prescription, 3) clinical review of pharmacotherapy, with analysis of need, effectiveness, safety, convenience for each prescribed drug, 4) active participation of the pharmacist in the multiprofessional bedside visit, 5) elaboration of PIs of clinical relevance and 6) recording activities developed in an internal form of the clinical pharmacy service.

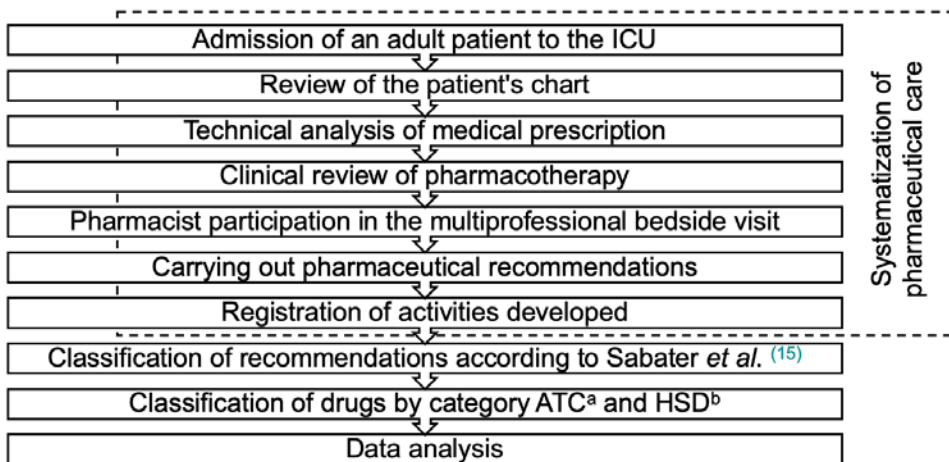
Patients aging 18 years or older, admitted on any day of the week and regardless of the length of stay in the ICUs, were included. The variables collected included gender and age of patients, ICU unit type, PIs made (accepted and not accepted) and drugs involved, acceptance of interventions and reasons for non-acceptance. PIs with incomplete registration of the analyzed variables or whose acceptance was unknown were excluded. Data were collected using a standardized form at the institution. Unaccepted

recommendations were also evaluated regarding the reason for non-acceptance in the following categories: 1) lack of justification, 2) hospital discharge or transfer within 24 hours after the recommendation, 3) verbally accepted, but did not change the prescription, and 4) prescriber judged the previous option as better.

PIs were analyzed for the categories of drug quantity and pharmacological strategy, using the classification proposed by Sabater *et al.*⁽¹⁵⁾ In the quantity of drug category, interventions were classified as 1) to change the dose (adjustment of the quantity of drug being administered right away) and 2) to change the dosing (change of frequency and/or duration of treatment). In the pharmacological strategy category, they were classified as 1) to add one or more drugs (addition of a new drug that was not in use by the patient), 2) to withdraw one or more drugs (abandon of the administration of a specific drug(s) among those used by the patient) and 3) to replace one or more drugs (replacement of any drugs among those used by the patient by others with different composition or of different pharmaceutical form or administration route).

Drugs involved in the recommendations were classified by the second level of the Anatomical Therapeutic Chemical (ATC) and by the categorization of High Surveillance Medicines (MAV), established by the Institute for the Practice of Safe Medication (ISMP) - a non-governmental, independent, non-profit organization that works to promote safe practices in the use of medicines and health products in Brazil.^(16,17) The age variable was categorized into the elderly and non-elderly groups, considering that, in Brazil, elderly are individuals aging 60 years or older.⁽¹⁸⁾

The data were collected and analyzed by pharmacists using Microsoft Excel®, version 2016. Numerical variables were presented as mean and standard deviation and categorical variables were exposed as frequency to investigate risk factors associated with acceptance of PIs. A significance level of 5 % was adopted. When investigating association between variables, Fisher's exact test was performed, due to the small sample size, in the Graph Pad Prism® statistical program, version 7.0d (USA). A scheme of the study's methodological flow is shown in Figure 1.



^a anatomical therapeutic chemical. ^b high-surveillance drugs.

Figure 1. Methodological flow diagram of the study carried out with pharmaceutical interventions carried out in the Intensive Care Units (ICU) of a university hospital in Fortaleza, Brazil.

Results

In this study, 305 patients were included, most of them male (55.1 %; n= 168), elderly (52.8 %, n= 161) and treated in the surgical ICU (51.4 %, n= 157). The mean age of the patients was 57.9 (SD: 15.9).

A total of 1,333 PIs were made in both ICUs, of which 16 (1.2 %) were excluded due to lack of information needed for analysis. Thus, 1,317 interventions were analyzed, generating an average of 4.31 recommendations per patient. Most interventions were related to male patients (54 %; n=711) and clinical ICU patients (69.5 %, n=915). The most prevalent PIs were to replace one or more drugs (28.0 %, n=396), to add one or more drugs (27.7 %, n=365) and to change the dose (24.8 %, n=327) (Table 1).

Table 1. Demographic data and pharmaceutical interventions associated with the acceptance of the study carried out with the pharmaceutical interventions performed in the Intensive Care Units (ICU) of a university hospital in Fortaleza, Brazil.

Variables (n=1317)	Accepted IP (n=1159)	No accepted IP (n=158)	<i>p</i>	RR	IC
Gender					
Female (n=606)	534	72	0.932	1.002	0.963-1.043
Male (n=711)	625	86			
Age					
Elderly (n=738)	654	84	0.443	1.016	0.976-1.058
No elderly (579)	505	74			
Intensive Care Unit (UCI)					
Clinical ICU (n=915)	847	68	<0.0001	1.193	1.128-1.261
Post-surgical ICU (n=402)	312	90			
High-Surveillance Drugs					
Yes (n=286)	267	19	0.001	1.079	1.038-1.122
No (n=1031)	892	139			
Pharmaceutical interventions (PI)					
To replace one or more drugs (n=369)	339	30	0.006	1.062	1.021-1.105
To add one or more drugs (n=365)	311	54	0.058	0.956	0.912-1.004
To change the dose (n=327)	284	43	0.492	0.982	0.937-1.031
To withdraw one or more drugs (n=224)	194	30	0.498	0.980	0.928-1.037
To change the dosing (n=32)	31	1	0.166	1.104	1.034-1.178
Therapeutic classes (with more than 5 % frequency)					
Antiinfectives for systemic use (n=317)	279	38	0.492	0.983	0.934-1.034
Blood substitutes and perfusion solutions (n=144)	136	8	0.019	1.076	1.025-1.130
Drugs for acid related disorders (n=102)	86	16	0.127	0.941	0.862-1.027
Vitamins (n=84)	72	12	0.355	0.960	0.876-1.051
Ophthalmologicals (n=80)	73	7	0.577	1.029	0.957-1.106
Stomatological preparations (n=79)	71	8	1.000	1.011	0.935-1.094

Regarding acceptance, 88.0 % (n=1159) of the recommendations were accepted. The recommendations that showed the highest prevalence of acceptance were to replace one or more drugs (29.2 %) and to add one or more drugs (26.8 %, n=311), followed by to change the dose (24.5 %, n= 284). Additionally, it was observed that 73.1 % (n= 843) of the accepted PIs were performed in the clinical ICU and that 57 % (n= 90) of the unaccepted ones were performed in the surgical ICU (Table 1). Overall, the most prevalent reason associated with non-acceptance (68.4 %, n= 108) was 'they thought the previous option was better'; this reason is also the most prevalent in each ICU individually. Other reasons included lack of justification (20.9 %, n=33) and verbal acceptance of the PI, but lack of prescription change (10.8 %, n=17).

A total of 150 different drugs were involved in the PIs, the most prevalent being anti-infectives for systemic use (24.1 %, n=317), blood substitutes and perfusion solutions (10.9 %, n=144) and drugs for acid related disorders, according to the ATC classification. A higher proportion of acceptance of the interventions was observed for the therapeutic classes: systemic corticosteroids (96.9 %; n=31/32), blood substitutes and perfusion solutions (94.4 %; n=136/144) and ophthalmologicals (91.3 %; n=73/80) (Table 1).

HSDs involvement was identified in 286 (21.7 %) of the PIs, which occurred mainly in the clinical ICU (74.5 %; n=213). Overall acceptance was 93.4 % (n=267). The main PIs involving HSD were to add one or more drugs (n=102), to replace one or more drugs (n=92) and to change the dose (n=55). The most prevalent therapeutic classes were blood substitutes and perfusion solutions (48.6 %, n=139), followed by antithrombotic agents (16.8 %, n=48), being the most frequent drugs potassium chloride, (n=47), magnesium sulfate (n=33) and unfractionated heparin (n=31) (Table 2).

Table 2. Main therapeutic classes and drugs involved by type of pharmaceutical interventions (PI) in the study performed in the Intensive Care Units (ICU) of a university hospital in Fortaleza, Brazil.

PI n (%)	Therapeutic class	n (%)	Most frequent drugs
To replace one or more drugs 369 (28.0 %)	Blood substitutes and perfusion solutions	52 (14.1 %)	Potassium chloride (n=17), Magnesium sulfate (n=14)
	Antiinfectives for systemic use	48 (13.0 %)	Vancomycin (n=10), Piperacillin/Tazobactam (n=7)
	Vitamins	40 (10.8 %)	Thiamine (n=16), Vitamin K (n=12)
	Others	229	-
To add one or more drugs 365 (27.7 %)	Blood substitutes and perfusion solutions	63 (17.3 %)	Potassium chloride (n=22), Magnesium sulfate (n=13)
	Antiinfectives for systemic use	50 (13.7 %)	Vancomycin (n=13), Piperacillin/Tazobactam (n=12)
	Stomatological preparations	42 (11.5 %)	Chlorhexidine 0.12 % (n=42)
	Others	210	-
To change the dose 327 (27.8 %)	Antiinfectives for systemic use	164 (50.1 %)	Meropenem (n=41), Piperacillin/Tazobactam (n=24), Vancomycin (n=24)
	Blood substitutes and perfusion solutions	19 (5.81 %)	Potassium chloride (n=6), Magnesium sulfate (n=5)
	Drugs for acid related disorders	18 (5.5 %)	Omeprazole (n=15), Ranitidine (n=3)
	Others	126	-
To withdraw one or more drugs 224 (17.0 %)	Drugs for acid related disorders	62 (27.7 %)	Omeprazole (n=56), Ranitidine (n=6)
	Antiinfectives for systemic use	43 (19.2 %)	Vancomycin (n=8), Meropenem (n=8)
	Analgesics	13 (5.8 %)	Tramadol (n=3), Metamizole (n=3), Morphine (n=3), Acetaminophen (n=3)
	Others	106	-
To change the dosing 32 (2.4 %)	Antiinfectives for systemic use	12 (37.5 %)	Amikacin (n=4)
	Vitamins	5 (15.6 %)	Vitamin K (n=2), Vitamin C (n=2)
	Calcium channel blockers	3 (9.4 %)	Amlodipine (n=3)
	Others	12	-

The associations of accepted and non-accepted PIs with the variables gender, elderly and non-elderly categories, inpatient units, PPM prescription, type of PI and therapeutic classes are described in Table 1. The Fischer test showed an association between the acceptance of the interventions when performed in the clinical ICUs ($p < 0.0001$, as opposed to surgical ICUs) and in the presence of HSD ($p = 0.0013$). In addition, significant associations were observed between acceptance of PIs and to replace one or more

drugs PI ($p=0.0062$) and the class blood substitutes and perfusion solutions ($p=0.0187$). Regarding other variables, there was no other statistically significant association (Table 1).

Discussion

This is the first study that evaluates PIs in ICU environments in Fortaleza using the classification proposed by Sabater *et al.* and evaluating possible factors associated with PIs acceptance.⁽¹⁵⁾ PI were performed by intensive care pharmacists as a strategy for optimizing pharmacotherapy and preventing adverse events, highlighting their important role in reviewing medical prescriptions. In addition, PI acceptance was associated with clinical ICU admissions, HSD prescriptions, to replace one or more drugs interventions and the therapeutic class blood substitutes and perfusion solutions.

The benefit of the pharmacist's involvement in the care of critically ill patients in this study can be observed by the large number of PIs ($n=1317$) and their high acceptance rate (88.0 %). Further, in comparison with the study performance by Fidelis *et al.* which explored PIs between 2010 and 2013 in the same ICU evaluated in the present study, it is noted an increase in the number of PIs and acceptance rates.⁽¹¹⁾ This finding is an indicator of improved quality of clinical pharmacy service and corroborates the role of the clinical pharmacist is well established in the ICUs of the hospital. Other studies report acceptance rates ranging from 64 % to 99.6 %.^(14,19-22) Factors such as prioritization of high-risk PIs, effective communication between different healthcare professionals and availability and openness to discussions from physicians may explain these acceptance rates.

Most of the PIs were performed for patients hospitalized in the clinical ICU (69.5 %), and a statistically significant association was found between clinical ICUs and accepted interventions, in as opposed to post-operative ICUs. Similar findings were reported in the study from Maciel *et al.*⁽¹⁹⁾ In fact, patients admitted to clinical ICUs use higher number of drugs, especially antimicrobials, have longer hospital stays and more clinical complications, when compared to patients admitted to the post-operative ICUs, thus being more susceptible to prescription errors and consequently to PIs. Furthermore, the clinical ICU has intensive care medical residents and a fixed daily bedside clinical visit time, which increase the possibility for discussions within the healthcare group and creation of bonds of trust between the pharmacist and the multidisciplinary care team.

The most prevalent PIs in this study were to replace one or more drugs (28 %) and to add one or more drugs (27.7 %), both considered as pharmacological strategies. Despite the difficulty in comparing studies due to the different classifications of PI, Reis *et al.* and Maciel *et al.* also reported prevalence rates of 18.9 % and 16.5 %, respectively, of these PIs.^(19,21) On the other hand, Bourne *et al.* reported higher prevalence rates of interventions related to add one or more drugs (28.2 %) and dose revision (25.8 %), while Fideles *et al.*, point out a predominance of the PI of dilution management (14.4 %) and dose adjustment (12.0 %).^(11,23) These variations in the prevalence rates of types of PI can be influenced by the patient population, clinical pathologies, professionals involved, maturity of the clinical pharmacy service and level of integration of the multidisciplinary ICU team.⁽¹¹⁾

A statistically significant association between the pharmacological strategy to replace one or more drugs and acceptance was observed ($p=0.0062$), being 29.2 % of the overall accepted PIs. On the other hand, there was a slight tendency of non-acceptance of PIs such as adding drug. These results indicate the need to assess the reasons associated with medical non-acceptance of certain types of PIs and to build and disseminate protocols at an institutional level that can lead to standardization of care and alignment of approaches.

Anti-infectives for systemic use formed the main class of drugs targeted by PIs (24.1 %), with the intervention 'Dose modification' (51.7 %) being the most frequent PIs for this class, and meropenem (18.9 %) and vancomycin (17.7 %) the main representatives. Similar results were described in the studies from Sereno *et al.* (33 %) and Fidelis *et al.* (52.7 %).^(11,24) In clinical practice, it is observed that antimicrobial doses are extremely important in the management of infections in critically ill patients, especially in cases of sepsis and septic shock. Moreover, other factors, such as obesity, positive fluid balance,

renal and/or hepatic failure are quite common and require frequent dosage adjustment, with daily monitoring, to avoid clinical worsening, emergence of toxicity or increased microbial resistance.⁽²⁵⁾

Errors in the use of systemic antimicrobial drugs have potential implications for both the individual and the population. The proper use of antimicrobial agents and their deprescription, when needed, with continuous application of pharmacokinetic principles and evaluation of bacterial resistance are key.⁽²⁶⁾ After initiation of antimicrobial therapy, daily assessment of the need, effectiveness and safety of the antimicrobials prescribed by a clinical pharmacist can reduce the risk of toxicity and guide actions to prevent and control bacterial resistance. In this context, the importance of implementing Antimicrobial Stewardship programs with the active participation of a clinical pharmacist is emphasized.⁽²⁷⁾

In this study, the involvement of HSDs was identified in 21.7 % of the PIs, showing a high acceptance rate of 93.4 %. The two HSDs most involved in PIs were potassium chloride and magnesium sulfate, both representing the therapeutic class blood substitutes and perfusion solutions, which were also associated with greater acceptance. Similar results were found in a prospective study carried out in Spain by Miarons *et al.*⁽²⁸⁾ In critically ill patients, electrolyte depletion is common, and a usual goal is to correct them to achieve normal serum values (mainly potassium and magnesium) and reduce the risk of ventricular tachycardia and other arrhythmias.⁽²⁹⁾ HSDs have a greater risk of causing more serious damage to patients if used incorrectly, when compared to other medicines. Prescribing HSDs requires double-checking prescriptions prior to administration, as well as identifying patients at high risk. Therefore, these drugs are potentially subject to greater institutional surveillance, becoming targets of PIs.⁽³⁰⁾

This study provides valuable information about PIs performed in two ICUs in Fortaleza, which may be useful for the methodological adequacy of similar studies. However, it has some limitations. The study was carried out in only one hospital, with few active beds, and the presence of scarce clinical data made it impossible to perform a broader assessment of the associated factors. Thus, these data cannot be extrapolated to other centers, rural hospitals, and institutions without the presence of a clinical pharmacist in the daily care of the patient in the ICU. In addition, the different classifications, and standardizations of PIs in different studies make it difficult to compare findings.

Conclusion

This study enabled the evaluation of several PIs performed in two ICUs using the PIs classification proposed by Sabater *et al.*⁽²⁰⁾ Further, we observed high PIs acceptance rates by the medical team, suggesting that the role of the intensive care pharmacist is consolidated in the hospital of the study. The acceptance of the interventions was statistically associated with admission to a clinical ICU (vs surgical), presence of high surveillance medicines, intervention to replace one or more drugs and therapeutic class blood substitutes and perfusion solutions. Finally, this study reinforces the role of the intensive care pharmacist in the review of medical prescriptions as a strategy for optimizing pharmacotherapy and preventing adverse events. In addition, we highlight the need for the use of PIs classifications that are standardized in the literature in order to simplify comparisons between studies.

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