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Description of a Comprehensive Medication Management service in an adult intensive care unit

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Abstract

Objective: To describe the results of a Comprehensive Medication Management (CMM) service offered to patients of an adult intensive care unit. **Methods:** A descriptive cross-sectional study of the results of the CMM service (April 2017 to November 2018). All the patients followed up in the CMM service were included in the sample of this study. The service was integrally based on the Pharmaceutical Care Practice and, therefore, used the Pharmacotherapy Workup (PW) method. the drug therapy Problems (DTP) were quantified and classified according to the PW method. The main medications involved in the DTP were also described, as well as the acceptance of the interventions by the multidisciplinary care team members and patients. **Results:** 146 patients were followed up during the study period, and 512 DTP were identified. Of these DTP, most were related to medication safety (37.7%) and to indication (37.5%). The main causes were high dose (23.0%, with emphasis on dose adjustments in cases of kidney injury), need for additional medication (18.9%, inclusion of medication for electrolytic, glycemic, and prophylactic control), and unnecessary medication (18.6%, emphasis on de-prescription of antibiotics that were not indicated). Most of the problems (23.6%) were related to the therapeutic class of systemic anti-infective agent. Of the total DTP detected, 81.6% were resolved. A total of 451 interventions were implemented, of which 92.9% (n=419) were with physicians. The majority of the interventions with physicians were accepted (n=344, 82.1%). **Conclusion:** A high number of drug therapy problems have been detected and resolved by the CMM pharmacist, with emphasis on safety problems. The high acceptability of the interventions reinforces the need for the service applied to the critical patient.

Keywords: critical care, medication therapy management, pharmaceutical services, drug utilization, intensive care units.

Descrição do serviço de Gerenciamento da Terapia Medicamentosa em uma unidade de terapia intensiva adulto

Resumo

Objetivo: Descrever os resultados do serviço de Gerenciamento da Terapia Medicamentosa (GTM) ofertado a pacientes de uma unidade de terapia intensiva adulto (UTI). **Métodos:** Estudo transversal descritivo dos resultados do serviço de GTM (abril de 2017 a novembro de 2018) oferecido a pacientes críticos de uma UTI adulto de um hospital municipal público. Todos os pacientes críticos acompanhados pelo serviço foram incluídos na amostra do presente estudo. O serviço baseou-se integralmente na prática profissional do *Pharmaceutical Care,* e, portanto, utilizando o método pharmacotherapy workup (PW). Os problemas relacionados ao uso de medicamentos (PRM) foram quantificados e classificados segundo o método PW. Também foram avaliados os principais medicamentos envolvidos nos PRM, assim como a aceitação de intervenções junto aos membros da equipe multiprofissional de saúde e aos pacientes. **Resultados:** um total de 146 pacientes foram acompanhados no período do estudo, com identificação de 512 PRM. Destes, a maior parte foi relacionada à segurança (37,7%) e indicação (37,5%) dos medicamentos. As principais causas foram dose alta (23,0%; com destaque para ajustes de dose em casos de lesão renal), necessidade de medicamento adicional (18,9%; inclusão de medicamentos para controle eletrolítico, glicêmico e profiláticos) e medicamento desnecessário (18,6%; destaque para retirada de antimicrobianos não indicados). A maior parte dos problemas (23,6%) relacionava-se à classe dos antimicrobianos de uso sistêmico. Do total de problemas detectados, 81,6% foram resolvidos. Para tal, foram realizadas 451 intervenções, sendo 92,9% (n=419) junto a médicos, que foram aceitas em sua maioria (n=344; 82,1%). **Conclusão:** Um número elevado de PRM foi detectado e resolvido por meio do GTM, com destaque para os problemas de segurança. A alta aceitabilidade das intervenções reforça a necessidade do serviço aplicado ao paciente crítico.

Palavras-chave: cuidados críticos, conduta do tratamento medicamentoso, assistência farmacêutica, uso de medicamentos, unidades de terapia intensiva.

Introduction

The intensive care unit (ICU) is a hospital sector that offers assistance to patients with critical clinical conditions. The patient's susceptibility to the occurrence of drug therapy problems (DTP) is greater in the ICU compared to other hospital units due to the serious nature of the diseases, polypharmacy, complex and high-risk pharmacotherapy, frequent changes in the use of medications, and instability in the clinical status of the hospitalized individuals[1,2]. As a consequence, pharmacotherapy is established as a determining factor in the evolution of these patients. Errors related to medication use are more serious in this sector and are frequently related to fatal outcomes and/or requiring additional life support measures[3-5].

The pharmacist's clinical performance in the care of critical patients in the adult ICU, as part of the multiprofessional team, is related to positive clinical and economic results, favoring the effectiveness and safety of pharmacotherapy[6,7]. The optimization of drug therapy helps in several critical points observed in the patient in intensive care, such as improvement of anticoagulant therapy, sedation, analgesia, antimicrobial therapy, glycemic control, and emergency actions[4,6]. In addition, it prevents the occurrence of adverse events associated with medications, which are capable of increasing the length of stay in the ICU and patient mortality .

The increase in mortality due to the occurrence of these events was demonstrated in a study from the 1990s[8] where the crude mortality rate was 3.5% in hospitalized patients who experienced an adverse drug event, compared to 1.1% in the group that did not have such a problem ($p<0.001$)[8]. Active strategies to ensure patient safety in the ICU are fundamental to prevent new injuries and future undesirable events and, among these, the role of the intensive clinical pharmacist in the care of critical patients is included.

Faced with this scenario, the Society of Critical Care Medicine and the American College of Clinical Pharmacy described the role of the clinical pharmacist in intensive care as indispensable for promoting the safety of critical patients, the pharmacist evaluation of all drugs in use being defined as a "fundamental activity" in terms of the appropriate indication, dose, drug interactions, and allergies, in addition to monitoring pharmacotherapeutic effectiveness and safety, with interventions when necessary[9]. In Brazil, through the National Health Surveillance Agency instituted in 2010 and the legislation that stipulates the minimum requirements for the functioning of ICUs, there is an effort to guarantee pharmaceutical care at the bedside[10].

Despite the evident demand and importance of the clinical pharmacist in the ICU, the performance of this professional in this hospital area is still scarce[11]. In this context, we highlight the potential of Comprehensive Medication Management (CMM) services, a clinical service whose theoretical and methodological foundations, derived from the Pharmaceutical Care Practice, propose the identification, resolution, and prevention of DTP in a standardized way. DTPs are defined as "undesirable events, or the risk of their occurrence, experienced by the patient, which involve or are suspected of involving drug therapy, inhibiting or delaying the achievement of the desired goals with pharmacotherapy"[12,13]. The evaluation of the medications in use by a patient is carried out utilizing a logical, systematic, and patient-centered process, allowing the professional to check if they are the most suitable for the clinical conditions, if they promote the best possible therapeutic results, if they are safe for the patient, and if they are used in the best possible way[12,13].

Although some authors have reported the beneficial results of the insertion of the pharmacist in ICU teams[6,7], the dissemination of Brazilian studies involving the performance and relevance of the clinical pharmacy service in this hospital sector is still scarce, especially involving the implementation and delivery of the CMM services. Therefore, this work aims to describe the results obtained by the pharmacist's performance, through the identification of DTP and interventions to resolve these problems, in an CMM service inserted in an adult ICU of a public hospital in the city of São Paulo, Brazil.

Methods

This is a descriptive study, with a retrospective analysis of the results of the CMM service offered to a single group of patients under critical care in the adult ICU of a public municipal hospital. This hospital, a reference in traumas, burns, and neurology sector in its region, has 464 beds, of which 20 make up the adult ICU. The CMM service was implemented in April 2017 as an integral part of the multiprofessional residency pharmacy program in the intensive care service.

In the present study, the sample analyzed was composed of all the ICU patients who were followed-up at the CMM service from April 2017 to November 2018. The inclusion of the patients in the service took place for convenience, without specific inclusion criteria, and according to an internal demand (e.g., referral of the patient by professionals of the unit) or by active search by the pharmacist who delivered the service. The patients were followed-up according to the availability of the clinical pharmacist, who was available between 3 and 5 days a week in the ICU under study. Thus, all patients that received CMM services in the ICU were included in this study, including those that had no DTP identified by the clinical pharmacist nor that had any interventions related to pharmacotherapy during their stay in the unit.

The care process used for offering CMM was based entirely on the Pharmacotherapy Workup (PW) method, in addition to attention to the concepts of holistic care, patient-centeredness, and the patient's subjective experience with the use of drugs, which are part of the Pharmaceutical Care Practice's framework proposed by Cipolle, Strand & Morley[12,13]. The PW method consists of an initial evaluation, followed by the elaboration of a care plan and, subsequently, the evaluation of the results obtained with the proposed interventions. Pharmacotherapy is evaluated sequentially in four stages. At each stage evaluated, it is possible to identify DTP, which are associated with: Indication (DTP1–Unnecessary medication; DTP 2 –Need for additional medication); Effectiveness (DTP 3–Ineffective medication; DTP 4–Dose too low); Safety (DTP 5–Adverse reaction to medication; DTP 6–Dose too high), and Convenience (DTP 7–Drug not convenient). A DTP, in turn, can have different causes involving pharmacotherapy.

In this way, all the medications in use and all the health problems of the patient at the time of follow-up were evaluated, for the purpose of identification, resolution, and prevention of DTP, which were classified according to the PW method. After the identification of the DTP, verbal interventions were carried out with the members of the health team or with the patient himself, aiming at their resolution.

All the information regarding the follow-up of the patients in the service, including the identified DTP and the interventions performed, were documented in specific records of the CMM service, which were used for data collection. For the characterization of the sample, the following variables regarding the patients and their pharmacotherapy were studied: gender, age (full years at the time of the first evaluation), lifestyle habits before hospitalization (smoking, alcohol consumption or use of illicit drugs–yes vs no), main cause for admission to the ICU (grouped by the International Statistical Classification of Diseases and Related Health Problems–ICD-10), number of health problems and medications used in the first CMM assessment, and final outcome of the patient (death, discharge from the ICU or still hospitalized in the ICU at the end of the study period). In addition, it was assessed whether the patient had any infection and/or creatinine clearance(estimated by the Cockcroft-Gault formula)[14] less than 60mL/min during the follow-up period by the CMM service, which often requires adjustment of the medication doses.

In order to assess the results of the CMM service, the following data were collected: number of evaluations performed, time of follow-up at the CMM service (days between the first and last evaluation or between the first evaluation and the final outcome of the patient–death/discharge), number and types of identified and resolved DTP, drugs involved in DTP (classified according to the Anatomical Therapeutic Chemical Classification System)[15], number of interventions performed (with team professionals or with the patient) and acceptability of the interventions performed with physicians. An intervention was considered "accepted" when the professional or the patient agreed to modify the pharmacotherapy to resolve the identified DTP .

The descriptive analysis of the variables was performed by determining the absolute and relative frequencies of the qualitative variables, and the means and standard deviations of the quantitative variables. The difference between the proportions of individuals for whom more than two (2) DTP (dependent variable dichotomized according to median) was compared according to the description variables of the sample profile (gender, age, and outcome in the ICU) using Pearson's chi-square test. The level of statistical significance was set at 5%. All the statistical analyses were performed using the Stata® statistical program, version 14.

This study was approved by the Research Ethics Committee of the hospital in which it was carried out and of the related educational institution, under CAAE records No. 80125417.6.0000.0081 and No. 80125417.6.3001.0073. As this is a retrospective data collection in medical records, the application of the Free and Informed Consent Form was waived.

Results

Characterization of the sample

Data was collected for 146 patients, obtained from 562 CMM assessments (mean: 3.9 ± 3.3 per patient; minimum: 1; maximum: 19). The mean follow-up time was 19.8 ± 21.1 days per patient (minimum: 1; maximum: 104). The mean age of the patients was 59.2 ± 19.1 years old (minimum: 18; maximum: 93), with more than half of the patients being 60 years old or older (n=78;53.4%). The report of smoking and/or alcoholism at some point before hospitalization was found for 46.6% (n=68) of the patients, while 11 patients (7.5%) had a history of illicit drug use.

Diseases of the circulatory system were the main diagnosis for admission to the ICU. In addition, 60 followed up patients came from postoperative (41.1%). During the follow-up period at the CMM service, 85.6% of the patients (n=125) developed some type of infection, and 65.8% (n=96) had a creatinine clearance level below 60mL/min. From the total of patients, 43.2% (n=63) died, while 50.7% (n=74) were discharged to the hospital wards (Table 1).

Table 1. Demographic and clinical characteristics of the study sample. (n=146)

Data	Total patients n (%)	Patients with DTP ≤ 2 n (%)	Patients with DTP > 2 n (%)	P-value
Gender				
Male	82 (56.2)	44 (53.7)	38 (46.3)	0.531
Female	64 (43.8)	31 (48.4)	33 (51.6)	
Age (years old)				
≤ 19	3 (2.0)	1 (33.3)	2 (66.7)	
20 – 39	25 (17.1)	16 (64.0)	9 (36.0)	0.407
40 – 59	40 (27.4)	21 (52.5)	19 (47.5)	
60 – 79	56 (38.4)	29 (51.8)	27 (48.2)	
≥ 80	22 (15.1)	8 (36.4)	14 (63.6)	
Outcome in the ICU				
Death	63 (43.2)	27 (42.9)	36 (57.1)	
Discharge	74 (50.7)	45 (60.8)	29 (39.2)	0.060
Hospitalized in the ICU at the end of the study	9 (6.1)	3 (33.3)	6 (66.7)	

ICU: Intensive Care Unit.

Most of the patients used five or more medications during admission to the CMM service (n=138; 94.5%), and 35.6% (n=52) used 10 or more medications. The mean number of drugs per patient at the beginning of the monitoring by the CMM service was 8.8 ± 3.1 (minimum: 2; maximum: 19). During follow-up, 82.9% of the patients (n=121) had at least one health problem in addition to their main cause of hospitalization, with systemic arterial hypertension (SAH) and/or diabetes (DM) being verified in 58.9% of the patients (n=86).

Identification of drug therapy problems

At least one DTP was identified in 76.0% of the patients (n=111) during the study period, totaling 512 DTP and a mean of 3.5 ± 4.0 per patient (minimum: 0; maximum: 24). Of these, 30.1% (n=154) were identified in the first CMM assessment. Taking into account the active principle of the drugs involved in DTP , ranitidine and heparin stood out, responsible for 9.8% (n=50) and 7.2% (n=37) of the total DTP identified, respectively. Regarding the therapeutic class, it was found that the highest proportion of DTP was related to systemic antimicrobials (23.6%; n=121) (Table 2). In this class, vancomycin (n=30; 24.8%), polymyxin B (n=25; 20.7%),meropenem (n=18; 14.9), and piperacillin/tazobactam (n=12; 9.9%) were the drugs most involved in DTP .

More than three quarters of the DTP identified were attributed to safety (n=193; 37.7%) and indication (n=192;37.5%). Among the safety DTP, the main cause was "Dose too high" (n=118; 23.0%), with the prevalence of DTP involving ranitidine (n=41; 34.8%), vancomycin (n=12; 10.2%) and meropenem (n=10; 8.5%) (Table 3)

Table 2. Number and percentage of medications involved in the drug therapy problems, grouped by the pharmacotherapy assessment stages, and by therapeutic class*

Therapeutic class	Indication n (%) N=192	Effectiveness n (%) N=80	Safety n (%) N=193	Convenience n (%) N=47	Total n (%) N=512
Digestive system and metabolism	31 (16.2)	27 (33.7)	49 (25.4)	13 (27.7)	120 (23.4)
Blood and hematopoietic organs	43 (22.4)	4 (5.0)	42 (21.8)	12 (25.5)	101 (19.7)
Cardiovascular system	29 (15.1)	7 (8.7)	37 (19.2)	11 (23.4)	84 (16.4)
Systemic hormonal preparations**	13 (6.8)	1 (1.3)	9 (4.6)	0 (0.0)	23 (4.5)
Antibacterials for systemic use	47 (24.5)	26 (32.5)	43 (22.3)	5 (10.6)	121 (23.6)
Musculoskeletal system	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nervous system	19 (9.9)	13 (16.3)	12 (6.2)	5 (10.6)	49 (9.6)
Antiparasitics, insecticides, and repellents	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Respiratory system	5 (2.6)	2 (2.5)	0 (0.0)	0 (0.0)	7 (1.4)
Others	2 (1.0)	0 (0.0)	1 (0.5)	1 (2.1)	4 (0.8)

*Classified according to the Anatomical Therapeutic Chemical Classification System. **Except sex hormones and insulins.

Table 3. Number of drug therapy problems, stratified by cause of occurrence (n = 512)

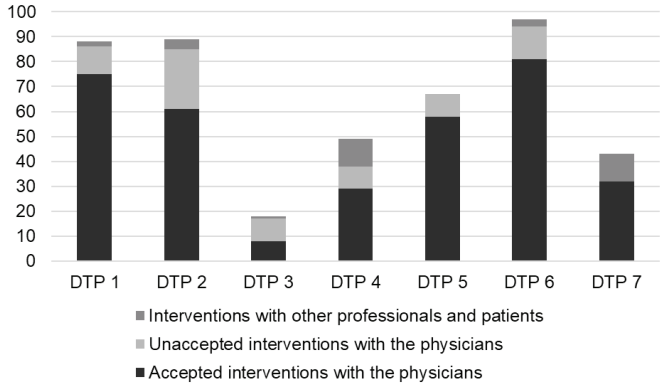
Causes of the DTP	Absolute value (%)
DTP 1 – Unnecessary medication	**95 (18.6)**
Absence of clinical indication	65 (12.7)
Dual therapy	16 (3.1)
Most appropriate non-drug therapy	12 (2.3)
Avoidable adverse reaction treatment	2 (0.4)
DTP 2 – Need for additional medication	**97 (18.9)**
Presence of an untreated clinical condition	57 (11.1)
Necessary preventive therapy	26 (5.1)
Synergistic therapy needed	14 (2.7)
DTP 3 – Ineffective medication	**20 (3.9)**
More effective medication available	12 (2.3)
Condition refractory to medication	6 (1.2)
Inadequate pharmaceutical form/product	2 (0.4)
DTP 4 – Low dose	**60 (11.7)**
Low dose to produce the desired effect	24 (4.7)
Frequency of administration less than necessary	21 (4.1)
Drug interaction that reduces the amount of drug available	8 (1.6)
Incorrect administration	7 (1.4)
DTP 5 – Adverse reaction to medication	**75 (14.6)**
Production of adverse effect not related to the dose	11 (2.1)
Allergic reaction	4 (0.8)
Medication not safe for the patient	50 (9.8)
Drug interaction causing an effect not related to the dose	2 (0.4)
Incorrect administration	8 (1.6)
DTP 6 – High dose	**118 (23.0)**
High dose	42 (8.2)
Frequency of administration higher than recommended	66 (12.9)
Treatment duration longer than necessary	4 (0.8)
Drug interaction causes a dose related reaction	1 (0.2)
Dose administered too quickly	5 (1.0)
DTP 7 – Not convenient	**47 (9.2)**
The patient prefers not to use the medication	1 (0.2)
Presence of a more economical alternative	6 (1.2)
The medication cannot be administered adequately	3 (0.6)
Medication not available for the patient	37 (7.2)

DTP: Drug therapy problems. *Classified according to the Pharmacotherapy Workup method proposed by Cipolle, Strand & Morley (2012).

Among the indication DTP , the cause related to "need for additional medication"(n=97; 18.9%) was the most frequent, with the recurrent recommendation for inclusion of potassium chloride (n=10; 10.3%), in addition to heparin, NPH insulin and acetylsalicylic acid, each responsible for 7.2% of the identified DTP (n=7). DTP related to "unnecessary medication" (n=95; 18.6%) were also frequent, with the recommendations for the interruption of vancomycin (n=10; 10.5%) and polymyxin B (n=7; 7.4%) from the patients' pharmacotherapy (Table 3).

Of the total DTP, 418 had been resolved at the end of the study period (81.6%). To this end, 451 interventions were performed with the health team or the patient. Of these, 419 were performed with physicians (92.9% of the interventions), of which 344 were accepted (82.1%). Figure 1 demonstrates the interventions performed due to DTP and their acceptability, with the highest proportion of unaccepted interventions referring to the inclusion of additional medication (n=24; 32.0%), with emphasis on acetylsalicylic acid (ASA) (n=3; 12.5%).

Figure 1. Number of interventions performed by the pharmacist and acceptability of the interventions by physicians, by type of DTP*.



*DTP: Drug Therapy Problem; DTP1: Unnecessary medication; DTP2: Need for additional medication; DTP3: Ineffective medication; DTP4: Dose too low; DTP5: Adverse reaction to medication; DTP6: Dose too high; DTP7: Non-adherence.

Discussion

Few studies demonstrate the results of clinical pharmacy services offered to critically ill patients and, to our knowledge, there are no studies that describe the results of CMM services in an adult ICU. The vulnerability of the patients admitted to the ICU and the multiplicity and dynamism of their clinical conditions and pharmacotherapy reinforce the need for the service, making this scenario a priority for the provision of pharmaceutical services on a continuous basis, and, more importantly, services that comprehensively assess all of a patient's health problems and medications in use.

Specifically in the ICU under study, patients were composed mainly of older adults and with a male prevalence, reflecting the global reality of Brazilian ICUs[16]. However, the mean follow-up time was even longer than that specified for the total length of stay in ICUs in several studies[3,17]. This characterizes a sample with a complex clinical profile, with a tendency to the chronification of its critical conditions, which, as a consequence, increases the length of stay in the ICU[18]. The high number of medications used (most undergoing polypharmacy – use of 5 or more medications – and excessive polypharmacy – 10 or more medications) and frequent evolution to death also reiterate the complexity of the patients (43.2% of the patients)[18]. Such factors reinforce the importance of inserting a clinical pharmacist and of implementing a service with the characteristics of the CMM in the unit under study.

The high number of identified DTP (n=512; mean of 3.5 per patient) also reinforces the relevance of the CMM service offered in the ICU. Additionally, eight out of ten patients had at least one DTP during the study period and, although a considerable number of these were detected in the first assessment (n=154; 30.1%), the majority (approximately 70%) was identified in subsequent evaluations. This suggests the need for the professional to continuously monitor the patients throughout their hospitalization period, as well as to know their clinical history and to evaluate the results of the interventions, instead of just performing specific assessments/interventions through analysis of prescriptions.

The compromised safety of pharmacotherapy was the main cause of the DTP identified (37.7% of the DTP). The positive impact of the clinical pharmacist's interventions on the safety of pharmacotherapy for critically ill patients has already been identified in an important study of the 90s, and by a meta-analysis that verified a 77% reduction in the occurrence of adverse events when performing pharmacist interventions (OR: 0.23; 95%CI: 0.11–0.48)[19,20]. In another study, where the problems related to pharmacotherapy identified in a pharmacy service in a Brazilian ICU were evaluated, antimicrobials were the drugs most associated with the detected problems. The main causes were inappropriate combinations and inadequate doses of medications[21].

Among the safety DTP, those related to the dose too high (23.0% of the DTP) stood out, as also identified in a study that described pharmacist interventions performed by the analysis of prescriptions of an ICU (46.7% of the total interventions)[17]. Also, similar to this study, the drugs most involved in high-dose DTP were those that require dose adjustment through changes in the patient's renal function (ranitidine, vancomycin, and meropenem)[17]. The importance of dose adjustment taking into account pharmacokinetic changes in patients with kidney injury is highlighted in the literature, including cost reduction[22]. However, it is important that the pharmacist go beyond the mere signaling to the health team regarding the need for dose adjustment, and that he prioritizes the individualization of his/her interventions according to the patient's clinical and pharmacotherapeutic profile, in addition to monitoring their evolution in the face of the interventions carried out.

The DTP related to the indication were the second most detected group (37.5%). The discontinuation of the use of unnecessary medications has an impact on reducing the risk of adverse events, drug interactions, medication errors, and costs associated with hospitalization[23]. The introduction of an additional medication, in turn, is associated with the professional's ability to detect untreated conditions or prophylactic measures that require the use of medications. In a study carried out in the United Kingdom, the introduction of a pharmacist specialized in providing care in the ICU was found to be related to the increased identification of problems associated with untreated conditions and drugs not indicated[6]. In this perspective, the CMM service is not limited

to the evaluation of drug interactions and/or the need for dose adjustment, and allows for an in-depth assessment of the indication of medications and/or the need for additional therapy, with a substantial potential to have a significant impact on the patient's clinical outcomes[12].

The need for additional medication (18.9% of the total DTP) was the most frequent cause of the indication DTP, and was more associated with the introduction of drugs present in clinical protocols commonly applicable to critically ill patients, such as the prophylaxis protocol for thromboembolism, control of stress hyperglycemia, electrolyte replacement, and cardiovascular prevention. The fact that ranitidine and heparin are the drugs most associated with DTP reflects this scenario, and highlights the need for the pharmacist to also assess the demand for additional pharmacotherapy, with emphasis on his role in adapting the prophylaxis of stress ulcers and venous thromboembolism, which are indicated for most patients admitted to the ICU[23].

Regarding the DTP resulting from the use of unnecessary medication (18.6% of the total DTP), antimicrobials stood out, which also constituted the therapeutic class most involved in DTP in the study. The indiscriminate use of antimicrobials is an alarming issue, as it is associated, among other problems, with the selection of resistant microorganisms in ICU's[24]. Another study also identified antimicrobials as the most involved class in pharmacists' interventions in an ICU[6]. In an assessment of the safety of drug use in two ICU's, antimicrobials were the drugs most associated with adverse drug events, accounting for 25% of the total[25]. Such results corroborate with the demand for the intensification of strategies for managing the use of antimicrobials and the insertion and intense performance of the pharmacist in this scenario, which can be developed through services that comprehensively assess patient's medications, such as CMM[24].

For the resolution of the identified DTP, interventions were carried out with the team and with the patient. About nine out of ten interventions were made with physicians, mainly due to the need to change the prescription when identifying a DTP. The interventions showed high acceptability (82.1%) by physicians, similar to that obtained in a clinical pharmacy service in a coronary care unit, in which 81.7% of the interventions were accepted, and to the proportions detected in a review study on pharmacotherapeutic follow-up in ICU's, which showed acceptance rates ranging from 71% to 98.4%[1,7]. This confirms the relevance of the interventions made by the pharmacist in the care process provided by the healthcare team.

The group of interventions associated with the recommendation for the introduction of a new medication (Needs additional therapy DTP) showed a greater number of unaccepted interventions by physicians, similarly to a study conducted in the Netherlands[26]. The drug most involved in this type of non-accepted intervention was ASA. This involves considerable individualization through clinical evaluation, since its insertion in pharmacotherapy, despite being guided by specific scores for cardiovascular prevention, is still based on controversial and scarce literature regarding its application in ICU's[27].

The present study is limited by the selection of a convenience sample and by the fact that it was performed in only one ICU. In addition, the clinical or economic impact of the interventions performed was not evaluated which, in the ICU context, although important, has limitations in its measurement, since the multiple factors and the great variability in the clinical status can influence the evolution of the critical patient. The absence of the clinical pharmacist some days of the week is also a limiting factor in the study, as it reduces the number of evaluations and, consequently, the ability to detect and resolve DTP. On the other hand, the high acceptability of the interventions indirectly demonstrates their clinical relevance. The importance of inserting the pharmacist in patient case discussions and interventions carried out verbally with the team is emphasized, as well as the comprehensive and holistic approach of the CMM practice, not previously described for the adult ICU scenario.

The limitations of the present study, however, are counterbalanced by the fact that its results refer to a real-world service, a format encouraged by the World Health Organization to evaluate services[28]. Additionally, according to the authors' knowledge, the literature lacks the description of the offer of CMM services in an adult ICU, having the potential to encourage the adoption of the practice in this relevant scenario in which patients with multiple pharmacotherapeutic needs are inserted. In the future, studies that evaluate the clinical impact of the service through control by multiple factors or using the control group may better elucidate its potential in critical care environments.

Conclusion

Through the CMM service, a high number of DTP was detected, with the majority of the patients followed-up in the ICU having at least one DTP. Of the identified DTP, the high percentage associated with safety problems stands out, which can result in negative developments for patients, worsening of the clinical conditions and increased mortality due to inadequate pharmacotherapy. The high acceptability of the interventions performed with the health team reinforces the importance of the clinical pharmacy service in this hospital sector, especially when considering the vulnerability of the monitored population. The high percentage of DTP resolved through the proposed interventions indicates the positive contribution of CMM in the evolution of patients admitted to the ICU, both favoring patient safety and the achievement of the therapeutic goals.

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All authors contributed to the conception and design of this study, data analysis and interpretation, writing of the article, critical review and final approval of the published version. In this way, they are also responsible for the information included in this work, ensuring the accuracy and integrity of any part of the paper.

Conflict of interest statement

The authors declare that there are no conflicts of interest regarding this article.

References

1. Hegele V, Heineck I. Role of Clinical Pharmacist in Adult Intensive Care Unit: A Literature Review. Rev Bras Farm Hosp Serv Saúde. 2014;5(1):19-24.
2. Kane-Gill SL, Dasta JF, Buckley MS, *et al.* Clinical Practice Guideline: Safe Medication Use in the ICU. Crit Care Med. 2017;45(9):e877-e915.
3. Silva AC, Souza DS, Perraud EB, *et al.* Pharmacotherapeutic follow-up in a respiratory intensive care unit: description and analysis of results. Einstein (São Paulo). 2018;16(2):eAO4112.
4. Fideles GMAF, Alcântara-Neto JM, Peixoto Júnior AA, *et al.* Pharmacist recommendations in an intensive care unit: three-year clinical activities. Rev Bras Ter Intensiva. 2015;27(2):149-54.
5. Silva LO, Oliveira Al, Araújo IB, *et al*. Prescribing errors in an intensive care unit and the role of the pharmacist. Rev Bras Farm Hosp Serv Saúde. 2012;3(3):6-10.
6. Richter A, Bates I, Thacker M, *et al.* Impact of the introduction of a specialist critical care pharmacist on the level of pharmaceutical care provided to the critical care unit. Int J Pharm Pract. 2016;24(4):253-61.
7. Barroso VPR, Caux TR, Nascimento MMG. Descrição de um serviço de farmácia clínica em uma unidade de cuidados coronarianos. Rev Bras Farm Hosp Serv Saúde. 2017;8(1):8-14.
8. Classen DC, Pestotnik SL, Evans RS, *et al.* Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277(4):301-6.
9. Rudis MI, Brandl KM. Society of Critical Care Medicine and American. College of Clinical Pharmacy Task Force on Critical Care Pharmacy Services. Position paper on critical care pharmacy services. Crit Care Med. 2000;28(11):3746-50.
10. Agência Nacional de Vigilância Sanitária (ANVISA). Resolução RDC no 7, de 24 de fevereiro de 2010. Dispõe sobre os requisitos mínimos para funcionamento de Unidades de Terapia Intensiva e dá outras providências [Internet]. Brasília (DF): ANVISA; 2010. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0007_24_02_2010.html. Accessed Nov 26, 2018.
11. Jurado LV, Steelman JD. The role of the pharmacist in the intensive care unit. Crit Care Nurs Q. 2013;36(4):407-14.
12. Cipolle RJ, Strand LM, Morley PC. Pharmaceutical Care Practice: The patient-centered approach to medication management services. New York: McGraw-Hill; 2012.
13. Ramalho de Oliveira D. Atenção Farmacêutica: da filosofia ao gerenciamento da terapia medicamentosa. São Paulo: RCN Editora; 2011.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
15. World Health Organization Collaborating Centre For Drug Statistics Methodology (WHOCC). Anatomical Therapeutic Chemical Classification (ATC Code) [Internet]. Norway: WHOCC. Available from: https://www.whocc.no/atc_ddd_index/. Accessed Nov 20, 2018.
16. Associação de Medicina Intensiva Brasileira (AMIB). UTIs brasileiras: Registro Nacional de Terapia Intensiva [Internet]. AMIB; 2017 Available from: http://www.utisbrasileiras.com.br/perfis-das-utis/caracteristicas-das-utis-participantes/. Accessed Nov 26, 2018.
17. Reis WCT, Scopel CT, Correr CJ, *et al.* Analysis of clinical pharmacist interventions in a tertiary teaching hospital in Brazil. Einstein (São Paulo). 2013;11(2):190-6.
18. Loss SH, Marchese CB, Boniatti MM, *et al.* Prediction of chronic critical illness in a general intensive care unit. Rev Assoc Med Bras. 2013;59(3):241-7.
19. Leape LL, Cullen DJ, Clapp MD, *et al.* Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA. 1999;282(3):267-70. Erratum in: JAMA 2000;283(10):1293.
20. Wang T, Benedict N, Olsen KM, *et al.* Effect of critical care pharmacist's intervention on medication errors: A systematic review and meta-analysis of observational studies. J Crit Care. 2015;30(5):1101-6.
21. Martins RR, Silva LT, Lopes FM. Impact of medication therapy management on pharmacotherapy safety in an intensive care unit. Int J Clin Pharm. 2019;41(1):179-88.
22. Ijo I, Feyerharm J. Pharmacy intervention on antimicrobial management of critically ill patients. Pharm Practice. 2011;9(2):106-9.
23. Mabasa VH, Malyuk DL, Weatherby EM, *et al.* A Standardized, Structured Approach to Identifying Drug-Related Problems in the Intensive Care Unit: FASTHUG-MAIDENS. Can J Hosp Pharm. 2011;64(5):366-9.
24. Agência Nacional de Vigilância Sanitária (ANVISA). Diretriz Nacional para Elaboração de Programa de Gerenciamento do Uso de Antimicrobianos em Serviços de Saúde [Internet]. Brasília (DF): ANVISA; 2017. Available from: http://portal.anvisa.gov.br/documents/33852/271855/Diretriz+Nacional+para+Elabora%C3%A7%C3%A3o+de+Programa+de+Gerenciamento+do+Uso+de+Antimicrobianos+em+Servi%C3%A7os+de+Sa%C3%BAde/667979c2-7edc-411b-a7e0-49a6448880d4. Accessed: December 27, 2018.
25. Carayon P, Wetterneck TB, Cartmill R, *et al.* Characterizing the Complexity of Medication Safety using a Human Factors Approach: An Observational Study in Two Intensive Care Units. BMJ Qual Saf. 2014;23(1):56-65.
26. Klopotowska JE, Kuiper R, Van Kan HJ, *et al*. On-ward participation of a hospital pharmacist in a Dutch intensive care unit reduces prescribing errors and related patient harm: an intervention study. Crit Care. 2010;14(5):R174.
27. Sociedade Brasileira de Cardiologia. I Diretriz Brasileira de Prevenção Cardiovascular. Arq Bras Cardiol. 2013;101(66):1-63.
28. Peters DH, Tran NT, Adam T. Implementation research in health: a practical guide [Internet]. Genebra: WHO, 2013. Available from: http://apps.who.int/iris/bitstream/handle/10665/91758/9789241506212_eng.pdf?sequence=1. Accessed: 11 Dec 2019.