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Conversion of intravenous to oral antibiotic therapy in an adult intensive care unit

Deise Luisa LOCATELLI[1], Carine Raquel BLATT[2], Maria Cristina WERLANG[2]

[1]REMIS UFCSPA/ISCMPA/SMSPA, [2]Departamento de Farmacociências, UFCSPA

Corresponding author: Werlang MC, werlangmc@gmail.com

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Abstract

Objective: To identify the possibility of alteration of intravenous (IV) to oral (PO) therapy for ampicillin/sulbactam and cefuroxime in adult patients treated in intensive care units (ICUs), and to describe the profile and consumption of antimicrobials prescribed for these patients. **Methods:** A descriptive, cross-sectional, and retrospective documentary study based on the analysis of electronic prescriptions and data from the electronic medical record of patients admitted to adult intensive care units in two hospitals, from July to August 2019. The consumption of antimicrobials was measured using the Anatomical Therapeutic Chemical/Daily Defined Dose (ATC/DDD) methodology per 100 beds-day. **Results:** Of the patients admitted to the study units, 23 (5.5%) received ampicillin/sulbactam or cefuroxime; the time of the ampicillin/sulbactam treatment was 7.25 (±2.07) days and, with cefuroxime, 8 (±1.73) days; 3 (13%) of the patients followed were eligible to switch therapy or sequential therapy, there was no physician acceptance of the conversion recommendation. The highest consumption was observed in the penicillins therapeutic group (112.5 DDD/100 beds-day) and meropenem drug (68.8 DDD/100 beds-day). **Conclusions:** Antimicrobial use is high in ICUs, which can be related to the clinical complexity and to the microbiological profile of the patients. The practice of converting IV antibiotic therapy to PO in critically ill patients was not present in this study; however, its use can contribute to patient safety.

Keywords: intensive care units, pharmacy service, hospital, antimicrobial stewardship.

Conversão da antibioticoterapia intravenosa para oral em unidade de terapia intensiva adulta

Resumo

Objetivo: Identificar a possibilidade de alteração da terapia intravenosa (IV) para oral (VO) de ampicilina/sulbactam e cefuroxima em pacientes adultos atendidos em unidades de terapia intensiva (UTI), bem como descrever o perfil e consumo de antimicrobianos prescritos a estes pacientes. **Métodos:** Estudo de delineamento documental, de caráter descritivo, transversal, retrospectivo, baseado na análise da prescrição eletrônica e nos dados do prontuário eletrônico dos pacientes internados em unidades de terapia intensiva adulta de dois hospitais, no período de julho a agosto de 2019. Mensurou-se o consumo dos antimicrobianos através da metodologia Anatomical Therapeutic Chemical/Dose Definida Diária (ATC/DDD) por 100 leitos-dia. **Resultados:** Dos pacientes admitidos nas unidades em estudo, 23 (5,5%) receberam ampicilina/sulbactam ou cefuroxima; o tempo de tratamento com ampicilina/sulbactam foi de 7,25 (±2,07) dias, e com cefuroxima 8 (±1,73) dias; 3 (13%) dos pacientes acompanhados foram elegíveis para a realização da *switch therapy* ou terapia sequencial sem aceite médico quanto a recomendação de conversão de via. Observou-se o maior consumo do grupo terapêutico penicilinas (112,5 DDD 100 leito-dias) e do fármaco meropenem (68,8 DDD/100 leito-dias). **Conclusões:** O uso de antimicrobianos é elevado em UTI, o que pode estar relacionado com a complexidade clínica e perfil microbiológico dos pacientes. A prática da conversão da antibioticoterapia IV para VO em pacientes críticos não se mostrou presente neste estudo, contudo o emprego da mesma pode contribuir com a segurança do paciente.

Palavras chave: unidades de terapia intensiva, serviço de farmácia hospitalar, gestão de antimicrobianos.

Introduction

Antimicrobials have a prominent role among the health technologies applied in the intensive care unit (ICU). The prescription of these drugs is reported for approximately 70% of the hospitalized patients,[1] constituting the second most used class of drugs in hospitals, and accounting for 20% to 50% of hospital expenses with medications. This wide use can also impact on the individual's microbiota and on that of the hospital setting, contributing to the emergence of bacterial resistance.[2]

The high use of antimicrobials is related to high rates of nosocomial infection and to a higher incidence of adverse reactions. The consumption of antimicrobials in ICUs is approximately 10 times higher than in other hospital units, due to the high rate of nosocomial infections that varies from 5% to 30%.[3-4] Regarding the occurrence of adverse reactions associated with medications, nephrotoxicity, hepatotoxicity, ototoxicity, and infusion reactions stand out, signaling the need to monitor the use of these drugs.

The rational use of antimicrobial therapy depends on several factors, such as the following: spectrum of the antimicrobial used, which must be selected according to the usual pathogens in the hospital setting and to the antibiogram; good tissue penetration capacity; less potential for resistance induction; adequate safety profile, and good cost-effectiveness.[5-7]

Stewardship programs are a set of measures used to manage the rational use of antimicrobials in hospitals, with the aim of reducing resistance to these drugs through the appropriate choice of the drug to be used for the treatment of a given infection, as well as dose, route of administration, and correct treatment time. Stewardship actions are planned in a multidisciplinary team, composed of clinical pharmacists, nurses and physicians, and are associated with a reduction in hospital mortality rate, length of stay, and costs.[2,8]

One of the actions related to the practice of stewardship is the conversion of antimicrobial therapy for intravenous (IV) use to an equivalent for oral use (PO). There are three types of conversion from IV-to-PO therapy: sequential therapy, switch therapy, and step-down therapy. Sequential therapy is defined as replacing the same antimicrobial from IV-to-PO; switch therapy is the conversion of an IV antimicrobial to PO, of the same class, but a different compound, with similar power; and step-down therapy is the conversion of antimicrobial IV-to-PO of another class, with a lower spectrum of action than the initial therapy.[9-10]

The benefits of converting intravenous to oral antibiotic therapy are numerous, such as the following: decreased infection rate related to health care; reduction in hospital stay; cost reduction; reduction of nursing workload; reduction of sharps; greater patient comfort; reduction of fluid overload, and lower incidence of phlebitis.[11-12]

To be a candidate for sequential therapy, the patient must have clinical conditions that allow for the conversion of antimicrobial therapy in a safe manner: hemodynamic stability is one of these factors, that is, the perfusion of vital organs must be adequate allowing for the absorption of the drug present in the gastrointestinal tract into the bloodstream; the markers used to verify hemodynamic instability are serum lactate levels and the use of vasopressor drugs such as noradrenaline and vasopressin. Other clinical factors to be analyzed are: afebrile body temperature; improvement of signs and symptoms of infection (leukocytosis and falling c-reactive protein [CRP]); good gastrointestinal absorption (absence of nausea, vomits, diarrhea, hypotension, gastroparesis, short bowel syndrome); available oral route and the type of infection, as infections where there is low tissue penetration of antimicrobials such as endocarditis, meningitis, and soft tissue infections, among others, are not suitable for the switch therapy strategy.[10,12]

Likewise, the antimicrobial used in the sequential therapy must present: oral formulation available on the market; good bioavailability for oral use; high systemic and tissue concentrations, and adequate minimum inhibitory concentration (MIC).[12]

There are few studies on the conversion of IV antibiotic therapy to oral in the ICU, which may be associated with the clinical severity of the patients, which makes it impossible for the drugs to be absorbed properly, as well as with the profile of the antimicrobials used in this hospital, many of them not having any oral formulation, or lacking a good bioavailability profile. However, some intravenous antimicrobials such as ampicillin/sulbactam and cefuroxime have equivalents for oral use with high bioavailability, enabling switch therapy for critically ill patients with the aforementioned clinical conditions. The clinical pharmacist can signal the possibility of converting antimicrobial therapy to the healthcare team, through the selection of critically ill patients suitable for such measure, contributing to patient safety and cost savings.[2,13]

Therefore, this study aims to identify the possibility of changing the route of intravenous administration to the oral route of ampicillin/sulbactam and cefuroxime in adult patients seen in intensive care units, as well as to describe the profile and consumption of antimicrobials prescribed for these patients.

Methods

This is a descriptive, cross-sectional, and retrospective study with a documentary design, based on the analysis of the electronic prescriptions and on the electronic medical record data of patients admitted to adult intensive care units of two tertiary-level hospitals belonging to a hospital complex in the city of Porto Alegre.

This hospital complex has approximately 1,223 beds in its nine care units. The units that make up this study were selected for convenience and are characterized by being a general adult ICU and another for adults and specialized in cardiology. The first ICU has 20 beds for the general adult specialty in a general hospital; and the second has 10 clinical beds and 12 surgical beds for adult patients in a hospital whose specialty is cardiology.

Among the daily activities of the clinical pharmacy service at this institution, there is the provision of guidance for the team to change the route of administration of: ampicillin/sulbactam and cefuroxime, from intravenous to oral route, to patients using these drugs for more three days and that fit the clinical conditions. The choice of antimicrobials met the designation of the Hospital Infection Control Service (*Serviço de Controle de Infecção Hospitalar*, SCIH) of the institution under study. Thus, this study included patients who used ampicillin/sulbactam and cefuroxime in the period from July to August 2019, and who were followed up by pharmacists from the clinical pharmacy service.

The following information was collected and analyzed: the reason for the patient's admission to the ICU, recommendation for changing the route of administration, acceptability of the intervention by the prescribing physician, and the patient's clinical outcome (hospital discharge and death).

For ampicillin/sulbactam, switch therapy interventions for amoxicillin/clavulanate were performed, while for cefuroxime, sequential therapy interventions were performed.

For the evaluation of the factors that contribute to the decision making for the realization of switch therapy and sequential therapy, the following laboratory tests were collected: microbiological culture, antibiogram, leukogram, and PCR measurement. In addition to these data, gender, age, reason for admission to the ICU, study antimicrobial, days of treatment with the antimicrobial, use of vasopressor medication, fasting recommendation, gastrointestinal absorption, use of enteral tube, and if the patient was in exclusive palliative care, according to previous studies.[14]

The sample size was calculated considering that one third of the patients admitted using intravenous antimicrobials are eligible for switch therapy.[15] By calculating the proportion estimation, a sample size of 85 patients was obtained, with significance level of 5% and an absolute precision of 10.

In addition to the data referring to the use of switch therapy and sequential therapy and their applicability in the ICU, the description of the antimicrobials in use in the ICUs during the study period was carried out in order to know the pharmacoepidemiological profile of these units. To this end, the antimicrobial consumption report was run, which reported the number of bottles dispensed per month for the units under study. The consumption of antimicrobials was calculated through the defined daily dose (DDD) per 100 beds-day for each month, using the Gomes and Reis formula, classifying the antimicrobials according to the Anatomical-Therapeutic-Chemical (ATC) classification, using the ATC/DDD method as recommended by the WHO.[15] For the application of the formula, the hospital occupancy rate of the study units was calculated and the DDD established for the medication was consulted according to the Norwegian Medicinal Depot – NMD (in grams); the consultation was carried out on the WHO Collaborating Center for Drug Statistics Methodology platform. The mean value of the monthly results found was calculated.

The collected data were entered into a Microsoft Excel® 2010 table and subsequently analyzed using descriptive statistics in SPSS, version 21.0. They were then submitted to descriptive statistical analyses. The categorical variables were described by frequency and the continuous variables were assessed for normal distribution using the Kolmogorov-Smirnov test. The variables with normal distribution were described as mean and standard deviation, and the variables that do not have a normal distribution, through median and interquartile range.

The study was approved by the Ethics Committee for Research with Adults of the institution under study, according to opinion No. 13101719.4.0000.5335.

Results

A total of 418 patients were admitted to these units; of these, 23 (5.5%) received the study antimicrobials. As for the characteristics of the sample, 12 (52.2%) were women, and the age group was 66.9 (±12.7) years old. The main reasons for ICU admission were the following: respiratory failure: 5 (21.7%), acute myocardial infarction: 5 (21.7%), sepsis/septic shock: 4 (17.4%), respiratory infection: 3 (13.0%), ischemic stroke: 2 (8.7%), immediate postoperative: 2 (8.7%), exacerbated chronic obstructive pulmonary disease: 1 (4.3%), and pleural effusion: 1 (4.3%).

During the study, 20 (87.0%) of the patients used antimicrobial ampicillin/sulbactam and 3 (13.0%) used cefuroxime. Of these, three patients using ampicillin/sulbactam had their treatment suspended after the fourth day of use due to the result of the microbiological culture, two patients had growth of *Staphylococcus aureus* and started a targeted therapy with oxacillin, and one patient had growth of *Moraxella catarrhalis*, starting therapy with cefuroxime. The treatment time with ampicillin/sulbactam was 7.25 (±2.07) days, and with cefuroxime, 8 (±1.73) days.

Regarding the rational use of antimicrobials, 6 (26.1%) of the patients had the treatment guided according to the antibiogram, while the majority of the patients had the empirical treatment: 15 (65%) of the patients had a negative microbiological culture and, for 2 (8.7%) of the patients, no microbiological culture was requested. The pathogens found were *Klebsiella pneumoniae*: 2 (8.7%), *Staphylococcus aureus*: 2 (8.7%), *Pseudomonas aeruginosa*: 1 (4,3%), and *Acinetobacter baumannii*: 1 (4,3%), *Moraxella catarrhalis*: 1 (4,3%). The samples were collected from different sites: Uruculture, 10 (43.0%); Blood culture, 7 (30.0%); Tracheal aspirate, 4 (17.0%); Sputum, 2 (9.0%); and Bronchoalveolar lavage, 2 (9.0%).

Only 3 (13.0%) of the patients followed-up were eligible for switch therapy or sequential therapy. There was no acceptance by the physician regarding the recommendation of route conversion, due to the clinical severity of the patient. The remaining 20 (87.0%) were not included for the exchange due to the following factors: use of vasopressor medication, 3 (13.0%); recommendation not to receive anything by mouth, 9 (39.1%); clinical condition that prevented good gastrointestinal absorption, 3 (13.0%); use of enteral tube, 14 (60.9%); leukocytosis, 10 (43.5%); high CRP levels, 8 (34.8%); and patient in exclusive palliative care, 2 (8.7%). Many patients had more than one clinical condition as mentioned above.

As an outcome, 17 (73.9%) of the patients were discharged from the hospital and 6 (26.1%) died.

The mean consumption of anti-infectives and their therapeutic groups, expressed in DDD/100 beds-day in general adult ICUs, cardiology clinic, and cardiac surgery is described in Table 1. It is observed that the total consumption of anti-infectives was 385.16 DDD/100 beds-day, with the predominance of the following therapeutic groups: penicillins, 112.48 DDD/100 beds-day; carbapenems, 74.97 DDD/100 beds-day; and cephalosporins, 55.24 DDD/100 beds-day, with meropenem, 68.76 DDD/100 beds-day, being the most consumed antimicrobial, followed by oxacillin, 44.92 DDD/100 beds-day, and by cefazolin, 41.15 DDD/100 beds-day.

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Table 1. Distribution of the monthly mean value of antimicrobials according to the ATC/DDD classification, used in the units under study from July to August 2019.

Therapeutic group Anti-infectious agent	DDD/100 beds-day			Total DDD/100 beds-day	Total DDD/100 beds-day per therapeutic group
	ICU 1	ICU 2	ICU 3		
Cephalosporins (J01D)					
Cefazolin (J01DB04)	0.57	0.66	39.92	41.15	55.24
Cefoxitin (J01DC01)	0.08	-	0.84	0.92	
Cefuroxime (J01DC02)	0.99	0.14	0.66	1.79	
Ceftriaxone (J01DD04)	3.18	-	-	3.18	
Cefepime (J01DE01)	1.45	1.02	0.77	3.24	
Ceftazidime/Avibactam (J01DD52)	1.92	0.59	2.08	4.59	
Ceftolozam/Tazobactam (J01DI54)	0.37	-	-	0.37	
Carbapenems (J01DH)					
Meropenem (J01DH02)	42.60	15.24	10.92	68.76	74.97
Ertapenem (J01DH03)	3.36	2.16	0.69	6.21	
Polymyxins (J01XB)					
Polymyxin B (J01XB02)	21.95	11.59	2.34	35.88	35.88
Penicillins (J01C)					
Ampicillin (J01CA01)	7.63	1.90	1.95	11.48	112.48
Oxacillin (J01CF04)	16.99	26.99	0.94	44.92	
Ampicillin+inhibitor (J01CR01)	8.72	12.13	2.64	23.49	
Piperacillin+inhibitor (J01CR05)	15.26	8.12	9.21	32.59	
Glycopeptides (J01XA)					
Vancomycin (J01XA01)	11.34	4.14	4.41	19.89	19.89
Aminoglycosides (J01G)					
Amikacin (J01GB06)	2.33	5.03	3.09	10.45	14.19
Gentamicin (J01GB03)	0.68	1.43	1.63	3.74	
Macrolides (J01FA)					
Azithromycin (J01FA10)	2.02	2.20	0.35	4.57	5.54
Erythromycin (J01FA01)	0.08	-	-	0.08	
Clarithromycin (J01FA09)	-	0.89	-	0.89	
Fluorquinolones (J01MA)					
Levofloxacin (J01MA12)	2.08	2.46	-	4.54	5.13
Ciprofloxacin (J01MA02)	0.24	0.08	-	0.32	
Norfloxacin (JO1MA12)	-	-	0.27	0.27	
Tetracyclines (J01AA)					
Tigecycline (J01AA12)	0.80	6.20	0.18	7.18	7.18
Sulphonamides (J01EC)					
Sulfamethoxazole/Trimethoprim (J01EE01)	0.37	2.39	-	2.76	2.76
Lincosamides (J01FF)					
Clindamycin (J01FF01)	-	-	0.53	0.53	0.53
Other antibacterials (J01XX)					
Linezolid (J01XX08)	2.38	2.45	0.46	5.29	16.19
Daptomycin (J01XX09)	6.62	1.22	3.06	10.90	
Imidazole derivatives (J01XD)					
Metronidazole (J01XD01)	1.57	0.68	0.79	3.04	3.04
Triazole derivatives (J02AC)					
Fluconazole (J02AC01)	4.32	0.14	0.14	4.60	7.15
Antimycotics (J02A)					
Voriconazole (J02AC03)	0.41	2.14	-	2.55	
Anidulafungin (J02AX06)	3.38	1.26	0.35	4.99	12.75
Amphotericin B (J02AA01)	7.76	-	-	7.76	
Antimycobacterial (J04)					
Dapsone (J04BA02)	7.70	-	-	7.70	7.70
Direct acting antivirals (J05AB)					
Acyclovir (J05AB01)	0.38	0.36	0.09	0.83	2.94
Ganciclovir (J05AB06)	1.13	0.98	-	2.11	
Neuroamidase inhibitor (J05AH)					
Oseltamivir (J05AH02)	1.60	-	-	1.60	1.60
Total	182.16	114.59	88.31	385.16	385.16

* DDD/100 beds-day (Daily dose defined by 100 beds-day); ICU 1 (general ICU); ICU 2 (clinical cardiological ICU); ICU 3 (cardiac surgical ICU)

Discussion

The present study aimed to identify the possibility of changing the route from intravenous to oral administration of the ampicillin/sulbactam and cefuroxime antimicrobials in patients admitted to the ICU, it was verified that 3 (13%) of the patients monitored were eligible to perform switch therapy or sequential therapy according to the clinical and laboratory criteria established in this study, but there was no medical acceptance regarding the recommendation for route conversion. The high complexity of the patients in this study may have been a barrier for the physicians to perform switch therapy or sequential therapy.

As barriers to the conversion from IV-to-PO therapy reported in the literature, there is the lack of protocols and institutional guidelines for performing switch therapy, and the lack of expected results, in addition to organizational factors.[16] Therefore, educational measures and the construction of institutional protocols and guidelines become important, in addition to their wide dissemination. Thus, the adoption of training and continuing education addressing the strategy of converting intravenous to oral antimicrobial therapy, could alleviate the impact of this type of barrier, and make this practice routine care in the ICU.

In this research, the intervention was planned for two antimicrobials, ampicillin/sulbactam and cefuroxime in an intensive care setting, which certainly contributed to the small sample size achieved, in view of the low consumption profile of these drugs in the ICUs. Another limitation found was a short period of data collection. The literature points to a significant acceptance of physicians to the recommendations for converting intravenous to oral antimicrobial therapy in nursing patients, as pointed out in a previous study, where of the 86.5% of the patients in the pre-intervention group who were fit for switch therapy, only 5.76% had route conversion, whereas for 84% of the patients in the post-pharmaceutical intervention group, 72% performed the conversion.[9] There are few studies on the conversion of intravenous to oral antibiotic therapy in critically ill patients, which reinforces the importance of seeking to know more about this therapeutic strategy, through studies with a longer follow-up and, therefore, a larger sample size.

Regarding the profile and consumption of the prescribed antimicrobials, the total consumption of anti-infectives was 385.16 DDD/100 beds-day. Data from a research carried out in three hospital ICUs in another Brazilian region showed an antimicrobial consumption of 346.48 DDD/100 beds-day,[17] similarly to the findings of the present study and higher than the consumption of 182.8 DDD/100 beds-day found in another place of the country.[18] When comparing different hospitals, the characteristics of each institution should be considered, such as the microbiota of the hospital setting and the epidemiology of the patients, in addition to the time when the study was carried out, as the pattern of antibacterial consumption changes over time, factors that may explain the differences found.[19]

The therapeutic groups of greatest consumption observed in this work were the following: penicillins, carbapenems and cephalosporins, similarly to recent research on antimicrobial consumption in the ICU, such as a surveillance study of antimicrobial consumption, carried out in an ICU in Serbia during a five-year period, which reported a high consumption of broad-spectrum cephalosporins and carbapenems.[20] In another surveillance survey conducted in Saudi Arabia, the consumption of antimicrobials in five ICUs for 33 months was measured, observing the highest consumption of the meropenem and piperacillin/tazobactam drugs, both belonging respectively to the class of carbapenems and penicillins.[21] While in a study carried out in Argentina, there was a high consumption of the therapeutic groups of penicillins and other beta-lactams, a group in which carbapenems and cephalosporins are included.[22] Carbapenems and cephalosporins are broad-spectrum classes of antibiotics and its high consumption in the ICU may be associated with the clinical severity of critically ill patients and with the risk of nosocomial infection, resulting in the use of empirical antibiotic therapy; however, the use of these medications can cause an adverse reaction to drugs and induction of bacterial resistance when irrationally employed.[23]

From the analysis of the data obtained, it can be seen that both ICUs have different profiles, the most prescribed antimicrobials for each unit under study were meropenem (general ICU), cefazolin (cardiac surgical ICU), and oxacillin (cardiac clinic ICU)).

The general ICU serves diverse and highly complex cases, so the high consumption of meropenem may be related to the use of empirical therapy for resistant bacteria, considering that the hospital under study has a high incidence of infections caused by KPC-producing enterobacteria, and that these carbapenemases have high MIC, making it necessary to use higher doses of this medication to obtain the desired therapeutic effect, which may have contributed to the DDD value found for this medication.

The cardiac clinical ICU showed a high consumption of oxacillin, which may be associated with the clinical picture of endocarditis and bacteremia caused by *Staphylococcus aureus*, one of the most prevalent pathogens found in this study.[24-25] It was observed that, in the cardiac surgical ICU, cefazolin was the most widely used antibiotic; the use of cefazolin in cardiac surgery is well documented in the literature, and may have contributed to the consumption found.[26-27]

It is worth highlighting the consumption of the latest generation antimicrobial, ceftazidime/avibactam, indicated for the treatment of enterobacteria with multidrug-resistant KPC carbapenemases. Throughout this study, at least one patient used this drug in the studied ICUs, which points to the need for interdisciplinary action between the clinical pharmacy and the SCIH in monitoring the use of this medication, in order to reduce selective pressure and costs.

The results obtained point to differences in the consumption of anti-infectives among the analyzed ICUs, and between different hospitals. The variability in the consumption of these drugs is due to the local epidemiology and to the microbiological profile of each hospital and, as verified, the microbiological profile of each unit. The calculation of antimicrobial consumption helps in monitoring the use of these drugs and in detecting deviations in consumption that can be more accurately analyzed. The importance of protocols and guidelines for the use of antimicrobials has been evidenced; the use of indicators such as DDD/100 beds-day has become an important resource for institutional quality programs.

Conclusion

In conclusion, it is observed that many patients who are able to receive antimicrobials orally complete the cycle of parenteral treatment, which demonstrates the need for continued education and multidisciplinary action to provide this daily care. In critically ill

patients, there are many barriers found for performing sequential therapy, due to the complexity of these patients, as soon as they reach control of the infectious condition and clinical stability, they are discharged from the ICU. However, recent studies on switch therapy in the ICU, conclude that this action can be a safe intervention, contributing to cost reduction and to a reduction of the hospitalization time.[28] Therefore, it is recommended to carry out future research studies with a prospective design, greater sample number, and intervention of the pharmacist with the team, in order to know the impact of this action on the quality of life of critically ill patients and on cost reduction.

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Collaborators

DLL, MCW, and CRB: project preparation; data collection, analysis and interpretation; writing and critical review of the article. Approval of the final version to be published and responsibility for all the information of the paper, ensuring the accuracy and integrity of any of its parts.

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Conflict of interest statement

The authors declare that there are no conflicts of interests in this article.

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