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Antimicrobial use assessment in an intensive care unit after Stewardship Program implementation

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Abstract

Objetivos: Avaliar o perfil de uso de antimicrobianos na unidade de terapia intensiva (UTI), após implementação do *Antimicrobial Stewardship Program* (ASP). **Métodos**: estudo do tipo antes e depois da implementação do programa, realizado de janeiro a dezembro de 2018, envolvendo pacientes com mais de 18 anos, que estiveram internados na UTI, com solicitação de análise microbiológica para apoio diagnóstico de infecção presumida ou confirmada e em uso de antimicrobianos. Foram comparados os resultados dos períodos anterior e posterior à implantação do ASP (1º semestre/2018 *versus* 2º semestre/2018). Os dados secundários foram obtidos por meio de prontuários e *software* da unidade de estudo. Foi feita a caracterização da distribuição dos pacientes e monitoradas as variáveis: DDD/1000 pacientes-dia, internados na UTI, número de solicitações de tratamento, média de uso de antimicrobianos por paciente e proporção do consumo de antibióticos, obedecendo à categorização AWaRe. Para análise estatística, foram utilizados os testes t-Student com variâncias desiguais, t-Student com variâncias iguais e teste Mann-Whitney. **Resultados**: No total, 461 pacientes foram incluídos no estudo. Observou-se que o meropenem foi o antimicrobiano com maior DDD/1000 pacientes-dia em ambos os semestres avaliados (696,67 ± 120,95 *versus* 481,08 ± 145,23), seguido da vancomicina (316,50 ± 59,89 *versus* 311,71 ± 89,52). No período pós-intervenção do ASP, houve redução significativa da DDD/1000 pacientes-dia para os antibióticos Meropenem (p = 0,020) e Polimixina B (p = 0,007) e aumento para Piperacilina/Tazobactam. Observou-se um total de 1.605 solicitações de tratamento antimicrobiano em 2018, com redução significativa após intervenção do ASP (147,50 ± 16,63 *versus* 120,00 ± 18,34, p = 0,022). Considerando a classificação *AWaRe,* os antibióticos mais utilizados em 2018, em ambos os semestres, corresponderam aos de “Vigilância” (64%), seguidos dos classificados como “Reserva” (21%) e por fim, os de “Acesso” (15%). **Conclusões**: os resultados apontaram a redução do uso de antimicrobianos, especialmente de antibióticos de amplo espectro, após a intervenção do ASP, o que era esperado, visto que esta é uma ferramenta importante no manejo da terapia antimicrobiana em pacientes acometidos por infecção em unidade de cuidados críticos.

Palavras-chave: gestão de antimicrobianos; resistência microbiana a medicamentos; anti-infecciosos.

Avaliação do perfil de uso de antimicrobianos em uma unidade de terapia intensiva após implementação do Programa *Stewardship*

Resumo

Objective: To assess the antimicrobial use profile in an intensive care unit after implementing the *Antimicrobial Stewardship Program* (ASP). **Method:** A before-and-after implementation program conducted from January to December 2018 in patients admitted to an ICU, over18 years old and who had microbiological analysis to support diagnosis of presumed or confirmed infection and antibiotic use. The results from the periods before and after implementing ASP were compared (1st semester 2018 *versus* 2nd semester 2018). The secondary data were obtained from hospital medical records and software of the unit under study. Patient distribution was analyzed, and the following variables were monitored: DDD/1,000 patients-day, admitted to the ICU, number of treatment requests, mean use of antimicrobials per patient, antibiotic consumption ratio, following the *AWaRe* classification. The Student’s t test with unequal variances was used for statistical analysis, as well as the Student’s t test with equal variances, and the Mann-Whitney test. **Results:** A total of 461 patients were included in the study. Meropenem was the most consumed antimicrobial in both semesters assessed (696.67 ± 120.95 versus 481.08 ± 145.23), followed by Vancomycin (316.50 ± 59.89 versus 311.71 ± 89.52) according to DDD/1,000 patients-days. For the ASP post-intervention period, a significant reduction in DDD/1,000 patients-days was evidenced for Meropenem (p = 0.020) and Polymyxin B (p = 0.007). There was a significant increase in the Piperacillin/Tazobactam variable in the post ASP period (p = 0.034). A total of 1,605 antimicrobial treatment requests were observed in 2018, with a significant reduction after the ASP intervention (147.50 ± 16.63 versus 120.00 ± 18.34, p = 0.022). Regarding the AWaRe classification, the most used antibiotics in 2018, in both semesters, corresponded to “Watch” (64%), followed by “Reserve” (21%) and finally, “Access” (15%). **Conclusion:** The findings showed a reduction in antimicrobial use after ASP application, particularly broad-spectrum antibiotics, which was expected since this is an important tool in managing antimicrobial therapy in patients affected by infection in the critical care unit.

Keywords: antimicrobial stewardship; drug resistance microbial; anti-infective agents.

Introduction

Antimicrobial treatment of infections was shown to reduce morbidity and to save lives.[1] However, the World Health Organization (WHO) has highlighted the growth of microbial resistance in this century as a severe threat to global health.[2-3] This problem results in more complicated infections, increased mortality, longer hospital stays, impaired surgical prophylaxis and other procedures, in addition to higher associated costs.[4]

The occurrence of infections due to resistant multi-drug (MDR) microorganisms[5] is being increasingly evidenced. If no effective measures are taken, the perspective is that, in these cases, mortality will reach 10 million people by 2050.[6] Managing the use of antimicrobials is indispensable to limit the development of resistance.[3]

The Antimicrobial Stewardship Program (ASP) aims at optimizing pharmacotherapy in the treatment of infections, offering the patients adequate therapies considering correct indication, dose and duration, thus contributing for the best outcomes possible and to the prevention of adverse events. This is an organizational approach to promote and monitor the thoughtful use of antimicrobials, preserving their future efficacy.[7] Antimicrobial management corresponds to a set of evidence-based efforts and strategies for quality improvement.[8,3] The implementation of ASP has generated satisfactory results from a clinical, epidemiological and economic point of view. Its adoption must be boosted in health units, mainly in Intensive Care Units (ICUs).[9]

In ICUs, the thoughtful use of antimicrobials is challenging, especially due to patient severity and to the microbiological profile of these units, characterized by MDR pathogens. In view of this complex scenario, ASP can contribute to the adequate use of these medications and to better care outcomes. Considering the era of microbial resistance and seeking for the best practices, antimicrobial management programs have been a strategic tool for this confrontation.[10] The empirical prescription of broad-spectrum antimicrobials has been progressively increasing in recent years and the measure of the impact of these drugs consumption on public health and the environment is complex and relevant, since their use depends on a series of strategic actions[11] and can be associated with the risks of adverse events.[16] This scenario suggests that effective interventions are necessary in order to avoid the abusive use of these technologies in health, and ASP corresponds to a model that has been shown to be successful,[12] capable of optimizing use, so necessary to face resistance.[13-15] The objective of the study was to assess the use profile of antimicrobials in ICUs after implementing *ASP*.

Methods

A before-and-after type of study was carried out before and after the development of the program, from January to December 2018, in a teaching hospital, linked to the Unified Health System (*Sistema Único de Saúde*, SUS) network, by the Pernambuco State Health Secretariat. The study locus is an acute care hospital, which has 833 beds and is a reference in neurosurgery and multisystem trauma, among other specialties, located in Recife, Brazil.

The hospital has a general ICU, with 28 beds for the care of critically-ill adult patients and has written therapeutic protocols for the treatment of the main Healthcare-Related Infections (HRIs) and the community. These protocols are elaborated in a joint fashion by the Hospital Pharmacy Service and the Commission for the Control of Hospital Infections (*Comissão de Controle de Infecção Hospitalar*, CCIH).

The sample consisted of patients over 18 years old, admitted to the ICU in 2018 with a diagnosis of presumed or confirmed infection and a request for microbiological analysis as diagnostic support, with or without isolation of microorganisms, using at least one antimicrobial. The exclusion criteria considered were patients who, for some reason, did not have their culture results released in 2018 or who were unable to consolidate the related data.

ASP was implemented in the ICU in 2018. In the first semester, the necessary infrastructure for the implementation of central ASP elements was created, while in the second, the actions were executed. Therefore, the study was divided into two phases: before the implantation (1st semester 2018) and after the implantation (2nd semester 2018) and the results were subsequently compared for measurement.

In the phase prior to implementation, the Checklist of the Centers for Disease Control (CDC) was applied, adapted, for situational diagnosis. The HRI microbiological profile and the use rates of invasive devices were identified with pharmacist's participation. A multidisciplinary team was defined to standardize the actions, made up by specialists in infectious diseases, an infectologist, pharmacists and pharmacy residents, a microbiologist, intensive care physicians, nurses and managers. With the pharmacists' participation, a protocol was elaborated for the empirical treatment of infections. The actions were announced and the team was trained. The pharmacists were actively involved in the execution of the multidisciplinary processes: daily review of the antibiotic therapy, indication, dosage, dilution and administration, in addition to pharmacokinetic monitoring (Vancomycin levels - conducted by the pharmac team, including a laboratory request), de-escalation, suspension of use, and bedside visits, among other control measures,[17,18]

The monitored variables correspond to the following: Defined Daily Dose (DDD) represented by DDD/1,000 patients-days admitted to the ICU, number of antimicrobial treatment requests, mean use of antimicrobials per patient, and proportion of antibiotic consumption, considering the AWaRe categorization.[19] This classification corresponds to a tool developed by the WHO to aid in decision-making about which antibiotics to use and when. It can be useful to reduce microbial resistance and guarantee access. The overall objective is to reduce the use of antibiotics in the Surveillance and Reserve group that refer to more crucial antibiotics and with a higher risk of resistance. This categorization specifically involves antibiotics; for this reason, it does not apply to the other antimicrobials under study.[19]

As for the distribution of studied patients, they were grouped according to the demographic characteristics (age and gender), the main type of medical intervention indicated for the control of the pathology, as to whether it was clinical or surgical, length of hospital stay and mortality, considering whether the patient had positive microbiological analysis result for multi-drug resistant (MDR) microorganisms or not.

The antimicrobials that were monitored and, therefore, ASP targets in the studied ICU, for having clinical and epidemiological importance, were subjected to the CCIH management measures. Those administered to the patients during their stay in the ICU were monitored, regardless of whether they had been treated with these agents before or after their stay in the ICU. The list consisted of 22 antimicrobials, 19 of which were antibiotics and 3, antifungals. Polymyxin B, linezolid, tigecycline and polymyxin E, as Reserve antibiotics; meropenem, vancomycin, piperacillin/tazobactam, cefepime, ceftriaxone, ciprofloxacin, levofloxacin, ceftazidime, teicoplamine, and moxifoxacin as Surveillance antibiotics, and oxacillin, amikacin, metronidazole, clindamycin and cefazolin, as Access antibiotics. Antifungals corresponded to micafungin, amphotericin B and fluconazole. The use of these antimicrobials was monitored month by month and, finally, the semiannual monthly mean was obtained.

For the calculation of DDD, each antimicrobial was considered individually, with a view to updating the values for adult patients with a mean weight of 70 kg, forecast by the WHO in 2019. Considering the WHO standardization, the results were expressed in DDD per 1,000 patients-days and the antimicrobials were listed according to the Anatomical-Therapeutic-Chemical (ATC) classification. The necessary reference data for the follow-up were obtained through the following electronic address (https://www.whocc.no/atc_ddd_index/), as well as from the documentary collection of the Hospital Pharmacy of the institution and the values of patients-days, informed monthly by the CCIH.

The mean number of prescribed treatments requests was also observed, while the patients were in intensive care, as well as the mean use of these medications per patient. The counting methodology considered the month of the treatment request. The results were expressed in monthly mean values, considering the evaluation semester (before and after the ASP intervention).

The variables referring to antimicrobials consumption were calculated independently by the Hospital Pharmacy Service using ancillary software. Secondary data were used, obtained through the medical records and software of the referred study unit and organized in the Microsoft Excel® program to be statistically normalized.

The statistical analysis took place through the following measures: mean and standard deviation, considering the semester or the type of evaluation. For the comparison between the periods, the following tests were adopted: Student's t with equal variances, Student's t with unequal variances or Mann-Whitney. When the data presented normal distribution, the Student's t test was chosen and when this hypothesis of normality was rejected, in at least one of the periods (semesters) analyzed, the Mann-Whitney test was used. The Shapiro-Wilk test was employed to verify normality and the Levene F test to identify equality of variances. The significance level adopted was 5%. The program for obtaining the calculations was IBM SPSS, version 23.[20-21]

The study was approved by the Research Ethics Committee of the hospital under study, according to opinion No. 2,632,961 (CAAE: 84019418.4.0000.5198).

Results

Of a total of 495 patients monitored, 461 met the inclusion criteria. Of these, 232 were assisted in the 1st semester of 2018 and 229 in the 2nd semester, corresponding to monthly means of 38.67 ± 9.24 and of 38.17 ± 5.23 (p = 0.910), respectively. The demographic and clinical variables of the patients included can be seen in Table 1.

The mean monthly DDD of the monitored antimicrobials, per 1,000 patients-days admitted to the study ICU, in both periods studied is shown in Table 2. The most used antimicrobial, in both semesters, was meropenem (696.67 ± 120.95 versus 481.08 ± 145.23, p = 0.020), with a significant reduction after the ASP intervention.

The second antimicrobial with the highest DDD, in both semesters studied, was vancomycin (316.50 ± 59.89 versus 311.71 ± 89.52, p = 0.915). Polymyxin B, the third most used antimicrobial in the period prior to the ASP intervention, became the fourth most used in the second semester, with a significant reduction (220.28 ± 31.65 versus 139.15 ± 48.91, p = 0.007). The antibiotic piperacillin/tazobactam also underwent an important change in use, with a significant increase observed in the post-ASP-intervention period (65.98 ± 73.04 versus 147.86 ± 37.05, p = 0.034).

The results of DDD/1,000 patients-days are expressed as monthly mean of the evaluated semester, standard deviation and p-value. The medications arrangement in the table followed the result of DDD/1,000 patients-days, corresponding to the second semester, in decreasing order of value.

There were 1,605 treatment requests with antimicrobials throughout 2018, 885 in the period prior to the ASP intervention and 720 in the subsequent period. There was a significant reduction in the mean monthly amount, after the program was implemented (147.50 ± 16.63 versus 120.00 ± 18.34, p = 0.022), as shown in Figure 1.

Table 1. Characteristics of the patients and hospitalizations in the Intensive Care Unit (ICU) in the previous and subsequent semesters to the implementation of the Antimicrobial Stewardship Program (ASP).

	First semester	**Second semester**	**p-value**
	Mean ± SD	**Mean ± SD**	
Mean No. of patients	38.67 ± 9.24	38.17 ± 5.23	p(1) = 0.910
Age mean (years old)	45.00 ± 2.61	43.17 ± 2.79	p(1) = 0.267
Male (No. of patients)	23.83 ± 10.13	25.33 ± 5.28	p(1) = 0.754
Female (No. of patients)	14.83 ± 7.05	13.00 ± 2.45	p(1) = 0.561
Clinical Intervention (No. of patients)	22.33 ± 7.99	12.33 ± 3.20	p(2) = 0.027*
Surgical Intervention (No. of patients)	16.33 ± 5.50	25.83 ± 3.87	p(1) = 0.006*
Mortality of all the cases (No. of patients)	45.95 ± 9.51	43.63 ± 11.79	p(1) = 0.716
Mortality of the cases with MDR isolates (No. of patients)	52.03 ± 10.89	44.15 ± 12.10	p(1) = 0.263
Hospitalization time of all the cases (days)	36.54 ± 5.98	34.87 ± 3.48	p(1) = 0.569
Hospitalization time of the cases with MDR isolates (days)	45.07 ± 6.13	44.39 ± 8.38	p(1) = 0.877

(*) Significant difference at the 5.0% level; (1) Student's t test with equal variances; (2) Student's t test with unequal variances

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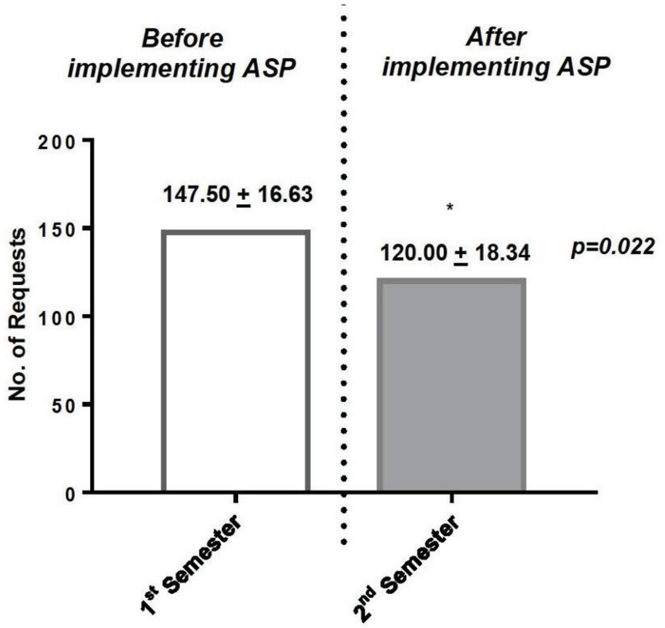
Table 2. Statistics of the variables related to the monthly mean of DDD/1,000 patients-days admitted to the Intensive Care Unit

Monthly mean of DDD/1,000 patients-days per antimicrobial			First semester	Second semester	p-value
			Mean ± SD	Mean ± SD	
ATC Code	**AWaRe classification**	**Antibiotics**			
J01DH02	Surveillance	Meropenem	696.67 ± 120.95	481.08 ± 145.23	p(1) = 0.020*
J01XA01	Surveillance	Vancomycin	316.50 ± 59.89	311.71 ± 89.52	p(2) = 0.915
J01CR05	Surveillance	Piperacillin and Tazobactam	65.98 ± 73.04	147.86 ± 37.05	p(2) = 0.034*
J01XB02	Reserve	Polymyxin B	220.28 ± 31.65	139.15 ± 48.91	p(2) = 0.007*
J01CF04	Access	Oxacillin	138.61 ± 133.33	119.99 ± 97.70	p(2) = 0.788
J01DE01	Surveillance	Cefepime	145.64 ± 80.82	119.16 ± 49.54	p(2) = 0.509
J01DD04	Surveillance	Ceftriaxone	114.33 ± 49.72	83.09 ± 41.17	p(2) = 0.263
J01GB06	Access	Amikacin	98.43 ± 23.11	77.44 ± 22.28	p(1) = 0.140
J01XD01	Access	Metronidazole	26.98 ± 18.54	31.90 ± 24.30	p(2) = 0.702
J01FF01	Access	Clindamycin	28.93 ± 28.88	17.07 ± 11.98	p(2) = 0.375
J01MA02	Surveillance	Ciprofloxacin	10.90 ± 6.28	14.80 ± 15.06	p(2) = 0.571
J01MA12	Surveillance	Levofloxacin	3.86 ± 9.46	11.78 ± 17.86	p(3) = 0.394
J01XX08	Reserve	Linezolid	4.48 ± 7.14	8.26 ± 13.91	p(3) = 0.818
J01DD02	Surveillance	Ceftazidime	0.00 ± 0.00	2.94 ± 4.71	p(3) = 0.394
J01DB04	Access	Cefazolin	0.27 ± 0.65	1.28 ± 2.04	p(3) = 0.589
J01XA02	Surveillance	Teicoplanin	0.00 ± 0.00	0.42 ± 1.03	p(3) = 0.699
J01AA12	Reserve	Tigecycline	4.37 ± 7.14	0.00 ± 0.00	p(2) = 0.165
J01MA14	Surveillance	Moxifloxacin	3.29 ± 7.44	0.00 ± 0.00	p(2) = 0.304
J01XB01	Reserve	Polymyxin E	0.72 ± 1.77	0.00 ± 0.00	p(3) = 0.699
ATC Code		**Antifungals**			
J02AC02		Fluconazole	114.99 ± 113.08	73.50 ± 58.93	p(2) = 0.444
J02AX05		Micafungin	8.99 ± 11.71	1.92 ± 4.70	p(3) = 0.310
J02AA01		Amphotericin B	0.61 ± 1.50	1.92 ± 3.36	p(3) = 0.699

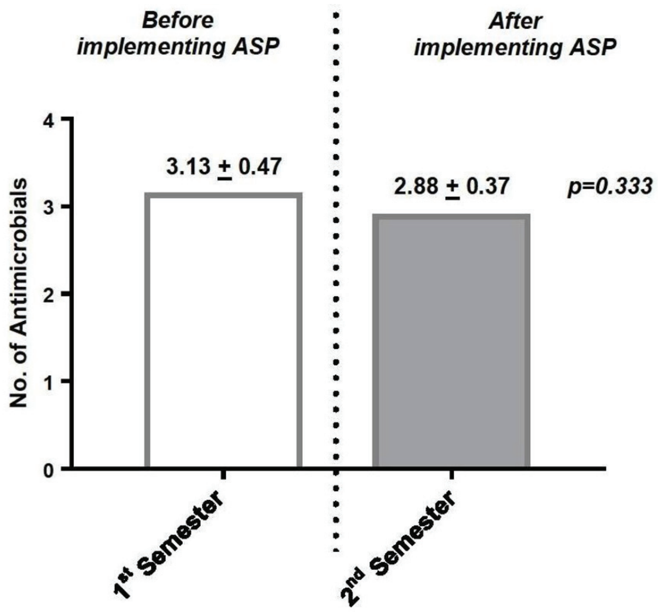
(*) Significant difference at the 5.0% level; (1) Student's t test with unequal variances; (2) Student's t test with equal variances; (3) Mann-Whitney test.; Antifungals are not categorized according to AWaRE, as this is a classification for antibiotics.

Figure 1. Monthly mean of antimicrobial requests in the Intensive Care Unit in the previous and subsequent semesters to the implementation of the Antimicrobial Stewardship Program (ASP).



*Student's t test (p<0.05).

Figure 2. Mean monthly use of antimicrobials in the Intensive Care Unit in the previous and subsequent semesters to the implementation of the Antimicrobial Stewardship Program (ASP) per patient.



*Student's t test with equal variances (p<0.05).

Treatment requests involving meropenem, amikacin, polymyxin B and piperacillin/tazobactam varied significantly, after comparing both semesters. Meropenem was the most requested, with a significant decrease in the mean monthly number of requests in the second semester (39.67 ± 4.37 versus 27.33 ± 6.44, p = 0.003). Amikacin was also less requested when the two periods were compared (11.33 ± 2.07 versus 8.50 ± 2.07, p = 0.039), as well as polymyxin B (16.67 ± 2.50 versus 9.33 ± 2.80, with p = 0.001). Piperacillin/Tazobactam had its monthly mean of requests increased in the second period (5.33 ± 5.05 versus 13.50 ± 3.78, with p = 0.010). The results are shown in Table 3 with semiannual monthly mean, standard deviation and p-value. The arrangement of the medications followed the number of treatment requests corresponding to the second semester, in decreasing order of quantity.

There was a reduction in the mean monthly number of antimicrobials used per patient, after the ASP intervention, from 3.13 ± 0.47 to 2.88 ± 0.37 (p = 0.333) (Figure 2).

Observing the AWaRe categorization, the pattern of antibiotic consumption was identified, without any significant proportional change throughout 2018, even after the implementation of ASP. Most of the antibiotics requested corresponded to the "Surveillance" type, totaling 993 (64%) treatments, 535 in the pre-intervention period and 458 in the post-intervention period. They were followed by the "Reserve" antibiotics, which were requested 326 (21%) times in 2018, with 191 cases recorded in the first semester and 135 in the second. Finally, the antibiotics classified as "Access" represented the least frequently prescribed group, with 223 (15%) requests, 125 in the period prior to the implementation of ASP and 98 in the subsequent period.

Table 3. Requests for antimicrobials in the Intensive Care Unit (ICU) in the previous and subsequent semesters to the implementation of the Antimicrobial Stewardship Program (ASP).

Variables			First semester	Second semester	p-value
			Mean ± SD	Mean ± SD	
ATC Code	AWaRe classification	Monthly mean of requests per antibiotic			
J01DH02	Surveillance	Meropenem	39.67 ± 4.37	27.33 ± 6.44	p = 0.003*
J01XA01	Surveillance	Vancomycin	31.00 ± 5.25	25.00 ± 6.48	p = 0.109
J01CR05	Surveillance	Piperacillin and Tazobactam	5.33 ± 5.05	13.50 ± 3.78	p = 0.010*
J01DE01	Surveillance	Cefepime	14.33 ± 6.44	12.67 ± 7.84	p = 0.696
J01XB02	Reserve	Polymyxin B	16.67 ± 2.50	9.33 ± 2.80	p = 0.001*
J01GB06	Access	Amikacin	11.33 ± 2.07	8.50 ± 2.07	p = 0.039*
J01DD04	Surveillance	Ceftriaxone	10.83 ± 3.76	7.83 ± 3.54	p = 0.186
J01XD01	Access	Metronidazole	3.83 ± 2.48	3.50 ± 3.08	p = 0.841
J01FF01	Access	Clindamycin	3.00 ± 2.00	2.00 ± 1.41	p = 0.341
J01CF04	Access	Oxacillin	2.50 ± 2.26	2.00 ± 1.79	p = 0.680
J01MA02	Surveillance	Ciprofloxacin	1.67 ± 0.82	1.33 ± 1.21	p = 0.588
ATC Code		Monthly mean requests per antifungal			
J02AC02		Fluconazole	4.67 ± 2.94	4.17 ± 2.14	p = 0.743
Monthly mean requests for the other antimicrobials			2.67 ± 1.37	2.83 ± 1.94	p = 0.867

*Student's t test with equal variances (p<0.05)

Discussion

The results showed a reduction in DDD for most of the antimicrobials monitored in the ICU studied in the period after the implementation of ASP. A number of research studies, also carried out in hospitals,[15] in hospitals presented similarities to our findings, showing an important reduction in the consumption of antimicrobials after effective interventions, especially in intensive care units.[22-25]

DDD is recommended by the WHO as an indicator for monitoring medication's use as well as for research development, being a reference measure for adult patients.[26] A European study also adopted this measure to monitor the consumption of antimicrobials, as a standardized strategy in hospitals that implemented ASP.[27] Meropenem was the most used antimicrobial during 2018. Studies carried out in ICUs identified carbapenems as the most representative antibiotics consumed.[12,28-30] The occurrence of infections caused by MDR microorganisms has become increasingly more frequent, influencing the increase in the consumption of broad-spectrum antibiotics. Among the bacteria of clinical importance, there are the gram-negative producers of ESBL, Adenosine 3',5'-cyclic monophosphate (cAMP) and extended-spectrum carbapenemase. Gram-positives, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, are also noteworthy. Infections caused by these microorganisms, in the context of public health, must be considered, as they cause the use of broad-spectrum antibiotics, prolonged hospital stay, and hospitalization in critical units, such as those that offer intensive care and even the use of invasive devices.[5] The empirical use of carbapenems has been progressively increasing in recent years, suggesting that effective interventions are necessary in order to avoid the abusive use of this class of antibiotics, and the Stewardship Program corresponds to a model that has shown to be successful.[12] The use of meropenem, as most prescribed, can be directly related to the problem of resistance. Exposure to this class of antibiotics creates selective pressure and ends up being a risk factor to worsen the profile of microbiological resistance.[31] Even though meropenem had greater use in both semesters studied, the implementation of ASP showed changes in its consumption, resulting in a significant reduction in the second semester. A number of studies have identified a reduction in the DDD of meropenem after implementing ASP[32], as well as similar results comparable to those found in the present study, showing a positive result of ASP in the use of broad-spectrum antimicrobials (carbapenems), with a significant reduction in DDD.[33] The identification of the impact on the consumption of meropenem was found in a research study which demonstrated that it is possible to replace this antibiotic with other therapeutic alternatives of a lower spectrum, and therefore the optimization of the use of the pharmacotherapeutic arsenal still available.[34]

The reduction in the DDD of meropenem occurred simultaneously with increased consumption of Piperacillin/Tazobactam according to the data analyzed. A study carried out in an Italian ICU also elucidated a tendency to reduce the use of carbapenems, parallel to the increase in the use of piperacillin/tazobactam, corroborating the findings of this study.[35] Vancomycin was one of the most used medications in both semesters under study. Similar results on the predominance of broad-spectrum antimicrobials use in ICUs were found in a study that evaluated the consumption of these mediations over a five-year period.[23] Both piperacillin/tazobactam[28] and vancomycin,[30] is reported in the literature as being widely used in this critical environment, corroborating our findings.

It is important to note that pharmacist participation in the... in the control of antimicrobial use has yielded a positive impact and must be supported. The reduction in antimicrobial use has shown to be directly related to the pharmacist participation in the care process in the care process.[36] The reduction in the total number of treatment requests was significant, after comparing both semesters. After the ASP intervention, the mean of antimicrobial use per patient was also reduced to 2.88 for each patient. Another national study verified that 42.5% of the patients studied received at least two of these medications, a mean value that is close to the one found in this study.[30]

Regarding the profile of antibiotic use, according to the AWaRe classification, the findings pointed to a predominance of Surveillance drugs, followed by those classified as Reserve and Access. The AWaRe structure is an important monitoring metric for combating microbial resistance and aims to ensure access to effective antibiotics.[37] This WHO classification, developed in 2019, as recommended by experts, works as an interactive reference tool for countries to improve antibiotic monitoring and ideal use. This categorization into Access, Surveillance and Reserve ratifies the importance of (monitoring) adequate use and its potential to cause microbial resistance. Antibiotics that do not have evidence-based indications can also be consulted in this database in order to provide guidance to the teams. Surveillance antibiotics were the most used in the ICU under study. According to the WHO, these medications have greater potential to induce resistance and encompass most of the highest priority agents among the antibiotics of critical importance in the clinical practice, in addition to presenting a relatively high risk of selection of bacterial resistance. They should therefore be prioritized as the focal point of Antimicrobial Stewardship, in the first- or second-choice empirical therapy for specific infectious diseases.[19]

According to the WHO, in a report that gathered worldwide information, referring to the period from 2016 to 2018 and corresponding to 65 countries and regions, the "Access" category represented more than 50% of the antibiotics consumed, while those of "Surveillance" presented a variation (20% to 50%), depending on the country. Those from "Reserve" accounted for less than 2% of the total antibiotics used by most developed countries.[38] This report was not specific for patients subjected to intensive care. Even so, this is a standardization measure that can aid in the monitoring of antibiotic use.[33] A cross-sectional multicenter study carried out in 56 countries and involving pediatric inpatients, not specifically in ICUs, receiving at least one antibiotic on the day of the research, found that the use of reserve antibiotics was low in all the countries evaluated.[38] The results showed that there was no statistically significant change, considering the length of hospital stay and mortality variables, involving or not isolation of MDR microorganisms, after comparing both semesters evaluated. A systematic review reported that, after the ASP intervention, lesser use of antimicrobials was observed in patients affected by infectious diseases, without causing an increase in mortality and also resulting in a reduction in length of hospital stay.[39] Other studies also confirmed that it is possible to reduce the use of broad-spectrum antimicrobials in the management of infectious diseases, without increasing the mortality rate, after implementing ASP.[40-42]

It is necessary to consider that the study was carried out in a single center and only reached the general adult ICU. Consequently, it is not possible to generalize the respective findings. Another relevant aspect corresponds to the period during which the research was developed, which possibly limited the number of patients and of relevant findings. Despite the similarity in the demographic profile of the patients under study, variations in the clinical profile may have influenced the pattern of consumption of antimicrobials, and some risk factors related to the acquisition of HRIs have not been evaluated. However, it is worth considering that the patients were treated as exposed to these risks in a similar way, in both semesters under study.

Conclusion

The results obtained suggest that the ASP intervention in the ICU was a good strategy to improve the use of antimicrobials in the hospital, and can be a fundamental for the optimization of these medications management in patients subjected to intensive care. Actions such as these must be encouraged and implemented in order to promote the optimized use of antimicrobials and, therefore, mitigate the advance of resistance, which represents a threat to global public health. The pharmacist can be a great ally in this process and, together with the healthcare team, contribute to the improvement of outcomes especially related to the prevention and treatment of HRIs. However, studies in other institutions and for longer periods are necessary to allow for a better evaluation of the results.

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Collaborators

VSB participated in the elaboration of the project, data collection, data analysis and interpretation, writing of the article, and critical review. DCGB, DESO, RDS, GMB, ALL, LCA, DMSA, VXB and DPS participated in the elaboration of the project, critical review and approval of the final version to be published. All the authors approved the final version to be published and assume responsibility for all 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 conf licts of interest regarding this article.

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