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Switch therapy of the association of ampicillin and sulbactam in a hospital complex in southern Brazil

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Abstract

Objective: To identify the frequency of pharmaceutical interventions performed and accepted by the physicians and the cost savings generated by the switch therapy of the association of ampicillin and sulbactam to the association of amoxicillin and potassium clavulanate in adult patients in a hospital complex. **Methods:** Observational cross-sectional study, based on the assessment of adult patients in intravenous use of the association of ampicillin and sulbactam for more than three days, from April to June 2021. Sampling was done for convenience. Interventions suggesting the change to the tablet of the association of amoxicillin and potassium clavulanate were performed through standard alert and evolution in the electronic health record of eligible patients. Acceptance was verified by follow-up of the new prescription. If not accepted, a new intervention was performed in 48 hours. Cost savings were calculated based on the average cost of medicines and medical supplies, available on the institution's computerized system. The collected data were analyzed using descriptive statistics. **Results:** A total of 322 patients were evaluable, of which 174 (54,0%) were considered eligible for the switch therapy. A total of 226 pharmaceutical interventions were performed, in which 14 (6,2%) were accepted by the physicians, generating savings of US$912,56. **Conclusions:** Pharmaceutical interventions recommending the switch therapy of the association of ampicillin and sulbactam had low adherence by the physicians, but, despite this, they presented a significant potential for cost savings. To obtain better results, it is necessary to promote the education of the clinical staff and improve communication between pharmacists and physicians.

Keywords: anti-bacterial agents; antimicrobial stewardship; pharmacy service, hospital; ampicillin; sulbactam; amoxicillin-potassium clavulanate combination.

Switch therapy da associação de ampicilina e sulbactam em complexo hospitalar do sul do Brasil

Resumo

Objetivo: Identificar a frequência de intervenções farmacêuticas realizadas e aceitas pelas equipes médicas e a redução de custos gerada pelo *switch therapy* da associação de ampicilina e sulbactam para a associação de amoxicilina e clavulanato de potássio em pacientes adultos de um complexo hospitalar. **Métodos:** Estudo observacional do tipo transversal, baseado na avaliação de pacientes adultos em uso endovenoso da associação de ampicilina e sulbactam por mais de três dias, no período de abril a junho de 2021. A amostragem foi feita por conveniência. As intervenções sugerindo a alteração para o comprimido da associação de amoxicilina e clavulanato de potássio foram realizadas por meio de alerta padrão e evolução no prontuário eletrônico dos pacientes elegíveis. O aceite foi verificado pelo acompanhamento de nova prescrição. Caso não fosse aceita, uma nova intervenção era realizada em 48 horas. A redução de custos foi calculada com base no custo médio de medicamentos e materiais médicos, disponível no sistema informatizado da instituição. Os dados coletados foram analisados por meio de estatística descritiva. **Resultados:** Um total de 322 pacientes foram avaliados, dos quais 174 (54,0%) foram considerados elegíveis para a *switch therapy*. Foram realizadas 226 intervenções farmacêuticas, das quais 14 (6,2%) foram aceitas pelas equipes médicas, gerando uma economia de US$912,56. **Conclusões:** As intervenções farmacêuticas recomendando a *switch therapy* da associação de ampicilina e sulbactam tiveram baixa adesão das equipes médicas, mas, apesar disso, apresentaram um potencial significativo de redução de custos. Para obtenção de melhores resultados, faz-se necessário promover a educação do corpo clínico e aprimorar a comunicação entre farmacêuticos e médicos.

Palavras chave: antibacterianos; gestão de antimicrobianos; serviço de farmácia hospitalar; ampicilina; sulbactam; combinação amoxicilina e clavulanato de potássio.

Introduction

Inappropriate use of antimicrobials favors increases in microbial resistance and in the costs associated with the treatment; therefore, control of prescriptions and consumption of this group of medications is indispensable.[1] Monitoring of antimicrobials is carried out through the stewardship program, a set of interventions aimed at ensuring proper use of antimicrobials based on the chosen drug, dose, frequency, administration route and length of treatment.[2]

Pharmacists, as part of the multi-professional team, are members of the stewardship program and act in different ways in order to optimize the use of antimicrobials: either through dose adjustment, therapeutic duplication warning, adequacy of treatment time and/or suggestion to switch from intravenous to oral therapy.[3] Change of the administration route can occur in three ways: sequential therapy, switch therapy or step-down therapy.[4] Sequential therapy is the substitution of a parenteral medication for its oral pharmaceutical presentation, while switch therapy is the transition to an equivalent oral drug of the same class and potency.[4] Step-down therapy is the change from an intravenous medication to an oral drug of another class or of the same class, but whose dose, frequency and action spectrum can be different.[4]

Conversion from injectable to oral antimicrobials is an effective and safe practice that must be performed with medications that present good bioavailability and tolerance.[5,6] It is recommended that the evaluation of the possibility of changing the administration route takes place 48 to 72 hours after initiation of the intravenous therapy.[7] The eligibility criteria for this change must be established by each institution, but usually consist in the ability to ingest and absorb the drug, good cooperation by the patient, absence of fever and vomiting, and improvement in the leukocyte count.[4,7]

The transition from parenteral to oral therapy provides advantages for the patient, namely: greater comfort, lower risk of adverse events related to the intravenous treatment, such as thrombophlebitis, and the possibility of home treatment, allowing for hospital discharge.[8,9] In addition to that, it also adds benefits to the health service, such as cost reduction (oral antimicrobials are generally cheaper and do not require medical supplies for use), reduced hospitalization time, reduced preparation and administration time of the medication and lower risk of medication errors, since injectable drugs present a higher risk of errors during their preparation and administration.[8-10]

Initiation of the antimicrobial therapy commonly occurs with parenteral medications, in order to control the severity of the infection and avoid a fatal outcome.[11] However, once the patient's clinical condition stabilizes, the use of intravenous antimicrobials may no longer be necessary, making it possible to switch to an oral pharmaceutical presentation.[11] The World Health Organization classifies excessive use of injectable pharmaceutical forms, when oral presentations would be more appropriate, as irrational use of medications.[12] Therefore, the oral route should be prioritized whenever possible, as this strategy does not alter therapeutic success, increases patient safety and reduces treatment costs.[3,13,14]

The intervention recommending changing the antimicrobial's administration route is usually initiated by pharmacists.[14] In the study by Sallach-Ruma *et al*. (2015), 52.0% of the pharmaceutical interventions performed were accepted by the medical teams, generating US$ 5,242 in savings.[6] In another research developed by Babonji et al (2021), the pharmacists analyzed patients in use of 17 medications, of which 10 were antimicrobials.[10] Of the interventions performed, 23.4% were accepted by the physicians, resulting in US$ 13,589.50 in savings, of which antimicrobials represented 93.5% of the value.[10] In this context, the objective of the study was to identify the frequency of pharmaceutical interventions performed and accepted by the medical teams and the cost reduction generated by the switch therapy from the ampicillin-sulbactam association to the amoxicillin-potassium clavulanate association in adult patients in a hospital complex.

Methods

This is an observational study of the cross-sectional type conducted in a teaching hospital complex, in the state of Rio Grande do Sul. Consisting in nine health care units (seven in the city of Porto Alegre) and more than 1,200 beds, it performs more than 6 million appointments per year, where 69.0% of the patients come from the Unified Health System (*Sistema Único de Saúde*, SUS).[15]

Ampicillin and amoxicillin are broad-spectrum penicillins, whereas sulbactam and potassium clavulanate are β-lactamase inhibitors.[16] The recommendation for the switch therapy from the ampicillin-sulbactam association to the amoxicillin-potassium clavulanate association was suggested by the Hospital Infection Control Service (*Serviço de Controle de Infecção Hospitalar*, SCIH) of the institution under study, being performed by clinical pharmacists.

The Clinical Pharmacy service of the health care units in Porto Alegre, comprised by 4 pharmacists and 4 Pharmacy residents, works in the stewardship program corresponding to several antimicrobials. For this study, the patients using the ampicillin-sulbactam association intravenously were monitored from April to June 2021, through a daily report that indicates the patients in use of this medication for more than three days.

Patients admitted to the health care units in Porto Alegre, except for the pediatric general hospital and Intensive Care Units (ICUs), were evaluated for the possibility of switching to the amoxicillin-potassium clavulanate association tablet. Therefore, sampling was for convenience. Patients who completed three days using the parenteral antimicrobial during weekends or on holidays were analyzed the following working day.

The two health care units in the inland of the state were not included, as they have different medical and pharmaceutical teams. The general pediatric hospital was excluded, due to the patients' difficulty in swallowing. In addition to that, the ICUs were also excluded since, in the study by Locatelli et al. (2020), carried out in the same hospital complex, there was a low percentage of patients eligible to switch from intravenous to oral antimicrobials, due to the severity of their clinical condition.[17]

The patients were categorized as "eligible" or "non-eligible" to change the treatment administration route by the Clinical Pharmacy service, according to parameters agreed upon with the SCIH. Patients who presented good oral acceptance of the diet, axillary temperature below 38°C and absence of vomiting in the last 24 hours were considered eligible. This information was verified in the patient's electronic medical record, as well as the following variables: age, gender, coming from the SUS, test result for the coronavirus 2019 disease (COVID-19), reason for using the antimicrobial, result of the microbiological culture, leukocyte count and C-reactive protein (CRP) dosage, both at baseline

and during the treatment. The improvement in the leukocyte count and CRP dosage after initiation of the intravenous therapy was not considered as a criterion for indicating a switch to oral therapy in this study, as these parameters were not present at a constant frequency for comparison between the patients. The Clinical Pharmacy service, responsible for the interventions, did not have autonomy to request laboratory tests or to change the antimicrobial.

The intervention was conducted in the treatment of the eligible patients by one of the clinical pharmacists or Pharmacy residents of the institution. Recommendation of the switch therapy was made by sending a warning to the medical team, by means of the institution's computerized system and record of the evolution. The warning consisted in a standard and brief text that overlaps on the screen, for 24 hours, when the medical team accesses the patient's electronic chart. In the text, it was suggested that the medical team evaluates the possibility of switching to the amoxicillin-potassium clavulanate association tablet. The evolution presented more details about the intervention, with the intention of remaining as a record in the patient's medical chart. Acceptance was verified by monitoring a new prescription with the amoxicillin-potassium clavulanate association tablet. In case it was not accepted and the patient continued using the antimicrobial intravenously, a new intervention was performed in 48 hours.

The cost reduction generated by the accepted interventions was calculated based on the mean cost of the medications and medical supplies, available in the computerized system of the hospital complex. The amounts were converted to US Dollars through the Central Bank of Brazil online currency converter on July 1st, 2021 (US$ 1.00 = R$ 5.005501). The value of the intravenous therapy includes the dosage prescribed and the cost of each administration of the ampicillin-sulbactam association (lyophilized powder and necessary medical supplies). The value of the oral therapy involves the dosage prescribed and the cost of each amoxicillin-potassium clavulanate association tablet. These costs are specified in Table 1. The length of the intravenous and oral treatments was recorded, in order to calculate the overall cost reduction for each patient.

The cost reduction that would occur if all the interventions were accepted (accepted interventions added to the rejected interventions) was estimated, considering that the rejected interventions would change to an amoxicillin-potassium clavulanate association tablet three times a day, as recommended in the literature and observed in the care practice.[18] In addition to that, the hypothetical length of the oral treatment was established starting one day after the first intervention and ending on the last day of intravenous antimicrobial use.

The data recorded by the Clinical Pharmacy service about the interventions performed were collected in a Google Sheets table. In order to control measurement biases, data collection was performed by one of the researchers, with specific training.

The data were analyzed by means of descriptive statistics employing the SPSS software, version 25.0. The categorical variables were described by means of absolute and relative frequencies and the continuous variables were assessed for normality using the Kolmogorov-Smirnov test. The variables with normal distribution were described as mean and standard deviation and, otherwise, as median and interquartile range. The cost reduction generated by the accepted interventions and the estimated cost reduction if all the interventions were accepted were described as mean and standard deviation. The categorical variables were compared between the patients by means of Pearson's chi-square test. Comparison of the patients' age was performed using Mann-Whitney's U test, according to data distribution, as well as the comparison of the daily and total cost reductions. Comparison of leukocyte count and CRP dosage at baseline and during the intravenous treatment was performed using the Wilcoxon test. The results with $p<0.05$ were considered significant.

The research project was approved by the Committee of Ethics in Research with Human Beings of the Federal University of Health Sciences of Porto Alegre (*Universidade Federal de Ciências da Saúde de Porto Alegre*, UFCSPA), in accordance with Opinion No. 40554720.1.000.5345, and by the Research Ethics Committee of the hospital complex under study, in accordance with Opinion No. 40554720.1.3001.5335.

Table 1. Cost of each intravenous administration of the ampicillin-sulbactam association (necessary medication and medical supplies) and of each oral administration of the amoxicillin-potassium clavulanate association

Administration	Medication/Material	Cost[1] (US$)	Cost/Adm (US$)
Ampicillin 1,000 mg + sulbactam 500 mg, intravenous	Ampicillin 1,000 mg + sulbactam 500 mg injectable powder	1.68	3.23
	Disposable needle	0.03	
	10 mL disposable syringe	0.06	
	Two 5 mL syringes filled with 0.9% PhS[2]	0.60	
	10 mL water for injection	0.06	
	Infusion equipment	0.37	
	Mean cost of diluents (0.9% PhS 100 mL and 5% SG 100 mL)	0.43	
Ampicillin 2,000 mg + sulbactam 1,000 mg, intravenous	Ampicillin 2,000 mg + sulbactam 1,000 mg injectable powder	4.05	5.60
	Disposable needle	0.03	
	10 mL disposable syringe	0.06	
	Two 5 mL syringes filled with 0.9% PhS[2]	0.60	
	10 mL water for injection	0.06	
	Infusion equipment	0.37	
	Mean cost of diluents (0.9% PhS 100 mL and 5% SG 100 mL)	0.43	
Amoxicillin 500 mg + potassium clavulanate 125 mg, oral	Amoxicillin 500 mg + potassium clavulanate 125 mg tablet	0.21	0.21

[1]Mean cost of the last purchases made; [2]Used for catheter flushing; Adm: Administration; 0.9% PhS: 0.9% Physiological Serum; 5% GS: 5% Glycated Serum.

Results

A total of 322 adult patients in use of the ampicillin-sulbactam combination intravenously were evaluated. One hundred and seventy-four (54.0%) patients were considered eligible for the switch therapy, while 148 patients (46.0%) were classified as non-eligible. The characteristics of the sample are shown in Table 2. One hundred and eight patients were categorized as non-eligible: 123 (83.1%) did not present good oral acceptance of the diet, 3 (2.0%) presented axillary temperature above 38°C, 6 (4.1%) presented vomiting and 16 (10.8%) did not qualify for other reasons, such as use of amoxicillin before initiation of the intravenous therapy, bacteria resistant to the ampicillin-sulbactam association, and surgical intervention plan. As for the comparison between eligible and non-eligible patients, there was a significant difference in age (p = 0.005), being higher in the non-eligible patients, and in positive diagnosis for COVID-19 (p = 0.029), being higher in the eligible patients.

Of the total of patients undergoing parenteral therapy with the antimicrobial, only 68 (21.1%) presented microbiological cultures with bacterial growth. It was possible to isolate two bacteria in the cultures from seven patients and three bacteria in the culture from one patient. The other 60 patients had only one bacterium isolated, totaling 77 identifications. The bacteria identified are presented in Table 2.

Table 2. Characteristics of the eligible and non-eligible adult patients for the switch therapy of the ampicillin-sulbactam association in a hospital complex in southern Brazil, from April to June 2021.

Information	**Total** N=322	**Eligible patients** N=174	**Non-eligible patients** N=148	**p-value**
Age (years old) median (IQR)	65 (54.00 to 75.00)	64 (47.75 to 72.00)	68 (57.00 to 77.75)	0.005[2]
Female gender[4] n (%)	165 (51.2)	91 (52.3)	74 (50.0)	0.681[3]
Hospitalization by the SUS n (%)	144 (44.7)	70 (40.2)	74 (50.0)	0.079[3]
Positive diagnosis for COVID-19 n (%)	27 (8.4)	20 (11.5)	7 (4.7)	0.029[3]
Reason for use n (%)				
Respiratory infection	72 (22.4)	41 (23.6)	31 (20.9)	
Urinary tract infection	62 (19.3)	37 (21.3)	25 (16.9)	
Surgical prophylaxis	54 (16.8)	29 (16.7)	25 (16.9)	
Skin infection	32 (9.9)	24 (13.8)	8 (5.4)	
Gastrointestinal infection	26 (8.1)	12 (6.9)	14 (9.5)	0.079[3]
Infection of the pancreas, liver or gallbladder	23 (7.1)	11 (6.3)	12 (8.1)	
Infection with undefined focus	14 (4.3)	6 (3.4)	8 (5.4)	
Bacteremia	11 (3.4)	5 (2.9)	6 (4.1)	
Others[1]	11 (3.4)	2 (1.1)	9 (6.1)	
Sepsis	10 (3.1)	3 (1.7)	7 (4.7)	
Pelvic infection	7 (2.2)	4 (2.3)	3 (2.0)	
Microbiological culture n (%)				
Empirical use with culture in progress	77 (23.9)	38 (21.8)	39 (26.3)	
Absence of bacterial growth	77 (23.9)	52 (29.9)	25 (16.9)	
Bacterial growth	68 (21.1)	30 (17.2)	38 (25.7)	
Total of identifications	77	32	45	
E. coli	32 (41.6)	18 (56.2)	14 (31.1)	
Enterococcus spp.	13 (16.9)	5 (15.6)	8 (17.8)	
Staphylococcus spp.	9 (11.7)	3 (9.4)	6 (13.3)	
Klebsiella spp.	7 (9.1)	2 (6.2)	5 (11.1)	
P. mirabilis	4 (5.2)	-	4 (8.9)	
Acinetobacter spp.	3 (3.9)	1 (3.1)	2 (4.4)	0.060[3]
Streptococcus spp.	2 (2.6)	2 (6.2)	-	
S. marcescens	2 (2.6)	-	2 (4.4)	
Enterobacter spp.	1 (1.3)	-	1 (2.2)	
P. aeruginosa	1 (1.3)	-	1 (2.2)	
Corynebacterium spp.	1 (1.3)	-	1 (2.2)	
A. hydrophila	1 (1.3)	-	1 (2.2)	
R. ornithinolytica	1 (1.3)	1 (3.1)	-	
Surgical prophylaxis	54 (16.8)	29 (16.7)	25 (16.9)	
Empirical use with no culture request	46 (14.3)	25 (14.4)	21 (14.2)	

[1]Oral infection, dental infection, osteomyelitis, endocarditis, thrombophlebitis and mediastinitis; [2]Mann-Whitney's U Test; [3]Pearson's chi-square test; IQR: Interquartile Range; SUS: Sistema Único de Saúde (Unified Health System), COVID-19: Coronavirus Disease 2019. [4]Dichotomous variable for which information of only one of the categories was presented.

Of the 322 patients evaluated, 201 (62.4%) had their leukocyte count and CRP dosage tested at baseline and during the treatment. The median leukocyte count (reference value of 3,600 to 11,000/µL) at the beginning of the intravenous therapy was 11,740/µL (7,610 to 15,495), while during the treatment it was 9,030/µL (6,320 to 12,300), with a significant difference (p<0.001) and a 23.1% reduction. The median CRP dosage (reference value of up to 3 mg/mL) at the beginning of antimicrobial use was 108.51 mg/L (39.88 to 197.88), while during the treatment it was 79.78 mg/L (36.55 to 142.79), with a significant difference (p<0.001) and a 26.5% decrease.

The frequency of the pharmaceutical interventions performed and their outcomes are presented in Figure 1.

Patients who had their treatment replaced by the amoxicillin-potassium clavulanate association tablet had a median age of 65.50 years old (53.50 to 70.00), 11 (78.6%) were female, 3 (21.4%) came from the SUS and 3 (21.4%) were diagnosed with COVID-19. Regarding the motivation for using the antimicrobial, 6 (42.9%) patients had respiratory infections, there were 4 (28.6%) with urinary tract infections, 3 (21.4%) with skin infections and 1 (7.1%) with a pelvic infection. Seven (50.0%) microbiological cultures were in progress, 6 (42.9%) had no bacterial growth and, in 1 (7.1%) culture, it was possible to identify the *E. coli* bacteria. The leukocyte count and CRP dosage were tested at baseline and during the treatment in 8 (57.1%) of the 14 patients with accepted interventions: 4 (50.0%) had a reduction in leukocyte count and CRP dosage, 2 (25.0%) had a reduction only in leukocyte count, and 2 (25.0%) had a reduction only in CRP dosage.

Between the group of patients with accepted interventions and those with rejected interventions, there was only a significant difference (p = 0.012) in the number of microbiological cultures in progress, being higher in the patients with rejected interventions.

The mean daily cost reduction per patient related to the change from intravenous to oral therapy is US$ 19.79 (± 3.51) and the mean total cost reduction per patient is US$ 65.18 (± 38.79). In all, cost reduction was US$ 912.56 with the accepted interventions.

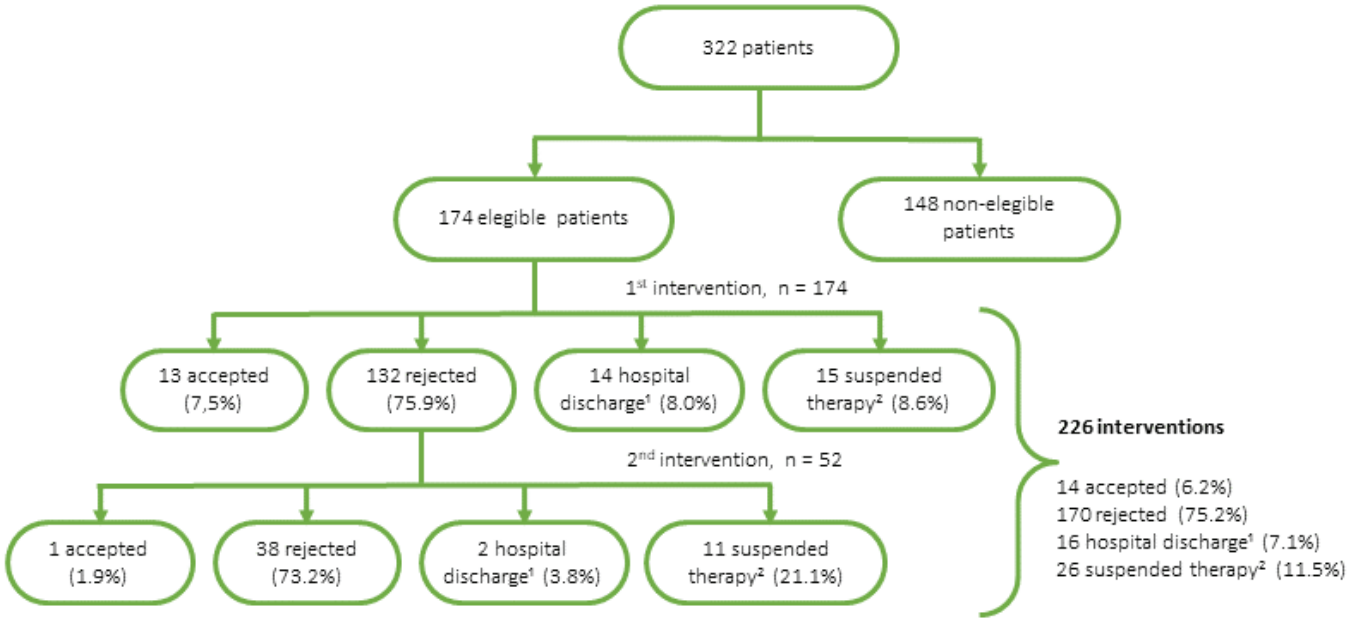
If all the recommendations for changing the treatment administration route were accepted (accepted interventions added to the rejected interventions), the mean daily cost reduction per patient would be US$ 19.69 (± 4.28) and the mean total cost reduction per patient would be US$ 81.56 (± 88.55). It is estimated that US$ 11,907.25 would be saved with the switch therapy of this antimicrobial in the study period, that is, a monthly cost reduction of US$ 3,969.08.

Discussion

It was verified that the pharmaceutical intervention recommending the switch therapy from the ampicillin-sulbactam association to the amoxicillin-potassium clavulanate association was performed in the treatment of approximately half of the patients in use of intravenous antimicrobials. The main reason for which the patients were considered as non-eligible was for not presenting good oral acceptance of the diet. The interventions accepted by the medical teams were not significant, but generated US$ 912.56 in savings over the 3 months under study, which could reach US$ 11,907.25 if all the interventions were accepted. The results of this study indicate the potential for carrying out the switch therapy and the need for a cultural change so that this optimization of the antimicrobial therapy is incorporated into the care practice.

The percentage of patients eligible to changing the antimicrobial administration route (54.0%) is similar to that observed in the study by Berrevoets et al. (2017), in which 52.0% of the patients were in suitable conditions for the oral therapy.[5] The main reasons for using the antimicrobial were respiratory infections and urinary tract infections, similarly to the findings of the study by Bonella et al. (2016).[19]

Figure 1. Frequency of pharmaceutical interventions recommending the switch therapy of the ampicillin-sulbactam association and its outcomes in a hospital complex in southern Brazil, from April to June 2021.



In a research study developed by Shrayteh *et al*. (2014), change of the antimicrobial administration route was more frequent in patients who had the bacteria causing the infection identified (p = 0.035).[20] Therefore, the low percentage of patients with identification of the pathogen in this study (21.1%) may have contributed to the low adherence to the interventions. This justifies the fact that more patients with rejected interventions had microbiological cultures in progress at the time of data collection (p = 0.012).

While 6.2% of the pharmaceutical interventions that suggested the switch therapy were accepted by the medical teams, 75.2% were rejected. The results are similar to those found in the study by Bonella *et al*. (2016), also carried out through a warning in the patient's electronic medical record and in a Brazilian hospital, in which 5.7% of the treatments were converted to the oral route and 70.2% were maintained intravenously.[19]

There are several obstacles regarding the transition from injectable to oral antimicrobials, namely: many physicians do not know all the benefits related to this practice or believe that patients who use the medication intravenously have a better clinical response.[8] In addition to that, there is some apprehension that adverse events may occur after the change, due to clinical inexperience with this strategy.[21] Therefore, continuing education and training are fundamental for greater compliance with this and other antimicrobial stewardship program actions.[3]

The studies by Berrevoets *et al*. (2017), Mouwen *et al*. (2020) and Sze and Kong (2017) provided educational actions for the physicians before implementing the interventions, suggesting a change in the antimicrobials' administration route.[5,22,23] The acceptance percentages were as follows: 73.8%, 83.9% and 97.4%, respectively.[5,22,23] Therefore, the adherence rate of this study could have been higher if educational programs and discussions with the institution's clinical staff had been carried out.[13]

However, there are also organizational obstacles to carrying out this activity, such as insufficient time for the physicians to review the intravenous therapy prescribed for each patient on a daily basis.[24] This study was carried out in a large-size teaching hospital complex, where there is difficulty in communication and adherence to care protocols and routines, due to the large number of professionals involved and their high turnover. In addition to that, the suggestion of the switch therapy does not occur through face-to-face or telephone contact and the pharmacist is not present in the inpatient units to carry out the intervention. The health professionals' stress, exhaustion and overload in the face of the COVID-19 pandemic may have contributed to the low acceptance of the interventions, as well as the warning fatigue in electronic medical records.[25,26]

The National Health Surveillance Agency (2017) points to cost reduction as a significant indicator for antimicrobial stewardship programs.[3] Based on the sample of patients in the 3 months under study, the annual savings if all the suggestions for the switch therapy of the ampicillin-sulbactam association were accepted would be US$ 47,628.96, which generates a positive impact for the hospital complex under analysis, in view of its philanthropic character. This value refers to the switch therapy of only one medication, but there is an opportunity for the pharmacist to act in the conversion from intravenous to oral treatment of other antimicrobials and therapeutic classes, such as antiulcer agents and antiepileptics.[4] Although it is not possible to compare the savings generated with other studies, due to local and time variations in value, cost reduction is one of the major advantages of changing the antimicrobials' administration route.[3,9]

The study limitation is the fact that the data were collected from the patients' electronic medical charts, in which there can be inconsistencies in the records, such as in the patient's axillary temperature.

It is believed that this study may bring about contributions to other services, since the protocol used can be implemented in other hospitals that use electronic medical records, in addition to being performed with other equivalent medications. This practice does not add any additional costs for the institutions that have the Clinical Pharmacy service, and is easy to reproduce.

Conclusion

Only a small percentage of the patients in use of the intravenous antimicrobial will be eligible for the switch therapy. Given that, it is fundamental that the intervention performed is assertive, so that there is acceptance by the medical team. In this study, the pharmaceutical interventions recommending the switch therapy of the ampicillin-sulbactam association had low adherence by the medical teams but, despite this, they presented a significant potential for cost reduction.

To obtain better results, it becomes necessary to implement and disseminate an institutional protocol in order to raise awareness among the teams involved in this process, promote education of the clinical staff, and improve communication between pharmacists and physicians. Each hospital must seek alternatives that are adequate to its reality to attain a high acceptance rate regarding the interventions.

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Collaborators

CMG, FZL and ALC: data analysis and interpretation, writing of the article and approval of the final version to be published, as well as responsibility for all the information included in the paper, ensuring accuracy and integrity of any of its parts.

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Conflict of interest statement

The authors declare no conflict of interest regarding this article.

References

1. World Health Organization. Antibiotic resistance. Available in: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Acessed on: 26th July 2021.
2. Fishman N. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA),

the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322-327. DOI: 10.1086/665010.

3. Agência Nacional de Vigilância Sanitária: Gerência de Vigilância e Monitoramento em Serviços de Saúde e Gerência Geral de Tecnologia em Serviços de Saúde. Diretriz nacional para elaboração de programa de gerenciamento do uso de antimicrobianos em serviços de saúde. Brasília: Anvisa; 2017. Available in: http://antigo.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?version=1.0#:~:text=Nesse%20sentido%2C%20a%20Ag%C3%AAncia%20Nacional,gerenciamento%20do%20uso%20de%20antimicrobianos. Acessed on: 24th Sept 2021.

4. Kuper KM. Intravenous to oral therapy conversion. In: Murdaugh LB (ed). Competence assessment tools for health-system pharmacies, 4. ed. Bethesda: American Society of Health-System Pharmacists, 2008: 347-360.

5. Berrevoets MA, Pot JHL, Houterman AE, *et al*. An electronic trigger tool to optimise intravenous to oral antibiotic switch: a controlled, interrupted time series study. Antimicrob Resist Infect Control. 2017;6(1):1-8. DOI: 10.1186/s13756-017-0239-3.

6. Sallach-Ruma R, Nieman J, Sankaranarayanan J, *et al*. Correlates and economic and clinical outcomes of an adult IV to PO antimicrobial conversion program at an academic medical center in midwest United States. J Pharm Pract. 2015;28(3):238-248. DOI: 10.1177/0897190013516367.

7. Akhloufi H, Hulscher M, Melles DC, *et al*. Development of operationalized intravenous to oral antibiotic switch criteria. J Antimicrob Chemother. 2017;72(2):543-546. DOI: 10.1093/jac/dkw470.

8. Béïque L, Zvonar R. Addressing concerns about changing the route of antimicrobial administration from intravenous to oral in adult inpatients. Can J Hosp Pharm. 2015;68(4):318-326. DOI: 10.4212/cjhp.v68i4.1472.

9. Cunha CB. Antimicrobial stewardship program perspective: IV-to-PO switch therapy. R I Med J. 2018;101(5):31-34.

10. Babonji A, Darwesh B, Al-Alwai M. Implementation of pharmacist-managed early switch from intravenous to oral therapy using electronic identification at a tertiary academic hospital. Saudi Pharm J. 2021;29(4):324-336. DOI: 10.1016/j.jsps.2021.03.006.

11. Chandrasekhar D, PokkaVayalil V. Cost minimization analysis on IV to oral conversion of antimicrobial agent by the clinical pharmacist intervention. Clin Epidemiol Glob Health. 2018;7(1):60-65. DOI: 10.1016/j.cegh.2018.01.001.

12. World Health Organization. Promoting rational use of medicines. Available in: https://www.who.int/activities/promoting-rational-use-of-medicines. Acessed on: 2nd Aug 2021.

13. Agência Nacional de Vigilância Sanitária. Uso racional de antimicrobianos e a resistência microbiana. Available in: https://www.anvisa.gov.br/servicosaude/controle/rede_rm/cursos/atm_racional/modulo1/uso_estrategias8.htm. Acessed on: 23rd July 2021.

14. Center for Disease Control and Prevention: The National Center for Emerging and Zoonotic Infectious Diseases. Core elements of hospital antibiotic stewardship programs. Atlanta: US Department of Health and Human Services, CDC; 2019. Available in: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf. Acessed on: 23rd Sept 2020.

15. Santa Casa de Misericórdia de Porto Alegre. Sobre a Santa Casa. Available in: https://www.santacasa.org.br/pagina/sobre-a-santa-casa. Acessed on: 4th Oct 2020.

16. Agência Nacional de Vigilância Sanitária. Antimicrobianos - bases teóricas e uso clínico. Available in: https://www.anvisa.gov.br/servicosaude/controle/rede_rm/cursos/rm_controle/opas_web/modulo1/penicilinas5.htm. Acessed on: 9th Sept 2021.

17. Locatelli DL, Blatt CR, Werlang MC. Conversion of intravenous to oral antibiotic therapy in an adult intensive care unit. Rev Bras Farm Hosp Serv Saude. 2020;11(3):0444. DOI: 10.30968/rbfhss.2020.113.0444.

18. Epocrates. Amoxicillin/clavulanate. Available in: https://online.epocrates.com/drugs/41901/amoxicillin-clavulanate/Adult-Dosing. Acessed on: 11th July 2021.

19. Bonella GF, Fontes AMDS, Jorge MT, *et al*. Assessment of an intervention aimed at early discontinuation of intravenous antimicrobial therapy in a Brazilian University hospital. Braz J Infect Dis. 2016;20(5):462-467. DOI: 10.1016/j.bjid.2016.07.002.

20. Shrayteh ZM, Rahal MK, Malaeb, DN. Practice of switch from intravenous to oral antibiotics. Springerplus. 2014;3(1):1-8. DOI: 10.1186/2193-1801-3-717.

21. Broom J, Broom A, Adams K, *et al*. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. J Antimicrob Chemother. 2016;71(8):2295-2299. DOI: 10.1093/jac/dkw129.

22. Mouwen AMA, Dijkstra JA, Jong E, *et al*. Early switching of antibiotic therapy from intravenous to oral using a combination of education, pocket-sized cards and switch advice: A practical intervention resulting in reduced length of hospital stay. Int J Antimicrob Agents. 2020;55(1):105769. DOI: 10.1016/j.ijantimicag.2019.07.020.

23. Sze WT, Kong MC. Impact of printed antimicrobial stewardship recommendations on early intravenous to oral antibiotics switch practice in district hospitals. Pharm Pract (Granada). 2018;16(2):855. DOI: 10.18549/PharmPract.2018.02.855.

24. Warburton J. Hodson K, James, D. Antibiotic intravenous-to-oral switch guidelines: barriers to adherence and possible solutions. Int J Pharm Pract. 2014;22(5):345-353. DOI: 10.1111/ijpp.12086.

25. Horta RL, Camargo EG, Barbosa MLL, *et al*. O estresse e a saúde mental de profissionais da linha de frente da COVID-19 em hospital geral. J Bras Psiquiatr. 2021;70(1):30-38. DOI: 10.1590/0047-2085000000316.

26. Agency for Healtchcare Research and Quality: Patient Safety Network. Alert fatigue. Available in: https://psnet.ahrq.gov/primer/alert-fatigue. Acessed on: 4th Aug 2021.