BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902024e23694

Article

Pharmaceutical interventions arising from the review of pharmacotherapy in hospital patients with COVID-19

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To characterize the main pharmaceutical interventions performed by reviewing the pharmacotherapy of hospital patients with COVID-19. This is a study carried out in a hospital center in the northern region of Santa Catarina, in which data were collected on pharmaceutical interventions resulting from the review of the pharmacotherapy of hospital patients with COVID-19, between April 2020 and June 2021. During the study period, a total of 16,675 medical presciptions were validated by pharmacists in theselected hospitalization sectors. These validations resulted in 1,108 pharmaceutical interventions, with the largest number related to drug dose adjustment (25.9%). Among the drugs, the class with the highest number of interventions was antimicrobials, especially Azithromycin with 23.5% of interventions performed, followed by Teicoplanin 23.9% and Meropenem 18.6%. Pharmaceutical interventions due to kidney function were also highlighted, as the disease is not restricted to damage to the respiratory system, but also presents complications in other organs, such as the kidneys. Through the review of pharmacotherapy and the pharmaceutical interventions resulting from this activity, clinical pharmacists played a key role in optimizing pharmacotherapy, in addition to promoting the safe use of medications.

Keywords: COVID-19. SARS-CoV-2 virus. Clinical pharmacy. Pharmaceutical care. Pharmaceutical services.

INTRODUCTION

The pandemic caused by the SaRS-CoV2 virus, originating in the city of Wuhan in China and responsible for the COVID-19 disease, triggers a type of severe acute respiratory syndrome (Visacri, Figueiredo, Lima, 2020). This disease demanded from all health professionals and services, reorganizations to institute ways to ensure effective and safe care for those infected. At the hospital level, the changes were great, including reorganizations of services and qualification of clinical pharmacists (Lynch, O'leary, 2020).

Clinical and hospital pharmacists, were together with the health team in the development of guidelines for the management of pharmacological treatments, due to the lack of specific treatments and the rapid evolution and updating of information (Mallhi *et al*., 2020). The activities aimed at for the analysis and review of pharmacotherapy through medical prescription are essential to minimize risks to patients, as they aim to detect possible problems related to medications and maintain constant communication between this professional and the health team (Hua *et al*., 2020).

Around seven thousand deaths are caused every year in the United States due to medication errors, which can also be described as errors in pharmacotherapy, a process that mainly involves prescribing, but also dispensing and using medicines. In Brazil, these problems are estimated to be the fifth leading cause of death (Rahn, Zonzini, Mendes, 2023).

Thus, the Pharmaceutical Care Network Europe (2019), highlighted among the positive results of the Pharmacotherapy Review, are the early detection of Drug-Related Problems and the suggestion of interventions, to guarantee the quality of the service provided.

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The positive results of pharmaceutical interventions regarding the rational use of medicines are defined and consolidated in the literature (Araujo *et al*., 2017; Cardinal, Fernandes, 2014). Furthermore, the publications demonstrated the important contribution of clinical pharmacist together with the health team (Hatah *et al*., 2013). However, in the context of the pandemic, the predominance of the subjects discussed it is about the management of pharmaceutical services with a focus on the supply of medicines (Al-quteimat, Amer, 2021) and little has been discussed about the clinical activities performed.

A study conducted in 2017, analyzed the profile of 506 clinical pharmaceutical interventions performed in an Intensive Care Unit (ICU), of a university hospital, where among the interventions related to medications, the "drug incompatibilities via Y-connection" stood out with 38.43% of the interventions performed, also the intervention of "need for therapy" with 14.16% and the "lack of the medication" with 8.99%. About the interventions not related to medications, the most frequent, was the "non-conformity in the prescription" with 29.51%. The acceptance rate was high, around 96.24%, demonstrating, therefore, the importance of the clinical pharmacist to achieve effective and safe therapeutic responses (Araujo *et al*., 2017).

Another study conducted in 2022, also analyzed pharmaceutical interventions in ICU, but in this context, in patients with COVID-19. In this study, data from 1,140 interventions were evaluated, which achieved 85.2% acceptance, and among the most performed interventions were those related to medication errors, such as "omission of doses or medications" with 357 interventions. The most involved medications were those related to the digestive tract and metabolism. Among the main limitations found, the dynamics and the high workload inherent to the pandemic by COVID-19 were highlighted. The study concluded that the pharmacist, as an integral part of the multiprofessional team, optimized the pharmacotherapeutic follow-up and helped in the detection and prevention of drug-related problems (DRPs) (Silva, Pimentel, Teixeira, 2022).

According to the Resolution of the Collegiate Board of Directors of the National Health Surveillance Agency (ANVISA) No. 585 of August 29, 2013, which regulates the clinical attributions of the pharmacist and gives legal grounds for the different clinical services, such as the review of pharmacotherapy, the current pharmacist, promotes the rational and safe use of medicines, through pharmaceutical care and interventions performed, with the aim of assisting in the safety and optimization of pharmacotherapy (Brazil, 2013).

Thus, this study sought to characterize the main pharmaceutical interventions carried out by reviewing the pharmacotherapy prescriptions of hospitalized patients with COVID-19.

MATERIAL AND METHODS

Design and characterization of the study site

This is a descriptive, retrospective, unicentric study with a cross-sectional design. The study was carried out in a private hospital, located in the region north of the state of Santa Catarina, south of Brazil. This hospital center is classified as a general hospital and was opened in the year 2001.

Before the pandemic by COVID-19, the place had 165 beds of infirmary and 19 Intensive Care Unit (ICU) beds. The inpatient sectors (infirmary) are divided by floors and differentiated according to the level of care. During the pandemic, there were numerous structural reorganizations for a better patient service, among the most important, are the growth of the number of ICU beds and also the isolation of some sectors, such as ICU No 01 and the Hospitalization Sector 2B, which were destined to receive only patients with COVID-19. During the course of the pandemic, the facility had 43 adult ICU beds, but currently has 175 beds, 20 of which are adult ICU beds.

The hospital had 14 pharmacists for the development of Clinical Pharmacy, Hospital Pharmacy, Oncology and Nuclear Medicine during the study period.

Review of pharmacotherapy

The review of pharmacotherapy is carried out based on the medical prescription through the Tasy Philips® computerized system, in which all pharmaceutical

interventions that have been carried out must be documented in the prescription history in the 'Clinical Pharmacy' module.

Subsequently, the indicators will be generated from the communication between the Tasy Philips® system and the Business Intelligence (BI) system. The latter is responsible for collecting, organizing and analyzing the data.

In order to carry out the review of pharmacotherapy with the aid of scientific databases and, consequently, evidence-based health, numerous known literatures were used, but the main platforms consulted were: Micromedex®, UpToDate® to verify the indication, doses and adjustments, as well as the treatment time and interactions of the prescribed drugs.

As for antimicrobial drugs, with regard to renal function mainly, the most consulted literature was The Sanford Guide, which was highly recognized in the area.

Analysis of pharmaceutical interventions

Pharmaceutical interventions, in the context of this study, are results of the pharmacotherapy review of the medical prescription, so they are part of the model of pharmaceutical activities linked to clinical services adopted by the site.

However, it is necessary to explain that only those interventions that resulted or, that would result (in case of interventions not accepted with or without justification) in changes in the medical prescription are considered as interventions performed.

Still for a better understanding, it is also necessary to mention that among these interventions, there are those that are performed with the physician, that is, that require previous contact with the prescriber for discussion and later alteration by the pharmacist, or by the prescriber, if necessary. And there are also those considered prescription adjustments. These last ones do not need previous medical contact for the changes to be performed by the pharmacist, being considered an autonomy of the pharmaceutical work.

Initially, all pharmaceutical interventions should be performed before the medical prescription is released for dispensing, so that there are no errors. Some examples of intervention classifications that must be performed through prior discussion with the physician are "Dose adjustment", "Request for insertion of non-prescribed medication", and "Request for Suspension of medication". Some examples of autonomous interventions by the pharmacist are "Adjustment in dilution (Volume/Diluent)", "Scheduling (Administration time)", and "Altered administration route according to patient's conditions".

It is noteworthy here that even though prior contact with the physician is not mandatory in some adjustment interventions, discussions about each one, when necessary for patient safety, aiming at the sum of knowledge, were always mutually encouraged.

It is also important to emphasize that when it is necessary to make changes in the prescription due to pharmaceutical interventions, the computerized system Tasy Philips®, in which the prescriptions and reviews are performed, allows the pharmacist himself, through the "Clinical Pharmacy" module, to make the adjustments, even before the prescription is released. Removing the need for a new prescription to be made by the physician and simplifying the flow of information.

Data collection and analysis

The data resulting from the pharmaceutical interventions carried out during the pharmacotherapy review, through the medical prescription in the Tasy Philips® computer program, in ICU no. 01 and in the hospitalization sector 2B, from April 2020 to June 2021, were organized and collected by the Business Intelligence (BI) system, through Excel® tables. In these tables contained the following variables: prescription number, hospitalization sector, type of historycal (type of pharmaceutical intervention), historycal data (manual observation, which the pharmacist can put as a complement to the historycal and the intervention performed), date and time of prescription release by the physician, date and time the prescription was released by the pharmacy's scheduling service and lastly, date, time, and name of the pharmacist responsible for releasing the review prescription for dispensing the drugs.

Ethics Committee Opinion

This study was approved by opinion number 5,190,408, the Research Ethics Committee of the Federal University of Santa Catarina (UFSC), through the Brazil Platform, CAAE 52672221,5,0000,0121, on October 1, 2021. All data were obtained by the researchers in a coded form, it being not possible to identify the patients.

RESULTS

During the 15 months of the study, which comprised the months of April 2020 to June 2021, the amount of 90,172 prescriptions were reviewed, considering the hospital as a whole, i.e., all inpatient sectors (ward) and Intensive Care Units (ICU). During this period, the pharmaceutical interventions reached around 98% acceptance.

When considering only the sectors selected for the study (ICU No. 01 and Inpatient Sector 2B) it is identified that the total number of prescriptions reviewed by pharmacists was 16,675 and that the months with the highest number of prescriptions reviewed were March 2021, with 1,595 prescriptions, followed by May with 1,413 and April of the same year with 1,408.

Regarding the comparison between the interventions performed with the physician and those of the pharmacist's autonomy, the interventions performed with the physician reached 63.4% of the total interventions performed, while those of the pharmacist's autonomy reached 36.6%.

The classifications, as well as the number of pharmaceutical interventions carried out, can be seen in Table I, where it can be seen that the total number of pharmaceutical interventions carried out during the study period was 1,108. The three main pharmaceutical interventions performed were: "Dose adjustment", with 287 interventions, followed by "Adjustment in dilution (Volume/Diluent)", with 209 interventions and, finally, the "Request for suspension of the drug" interventions, with 141 interventions.

TABLE I - Classifications and quantities of pharmaceutical interventions performed in the study sectors

	Types of pharmaceutical interventions	Amount
Interventions with the physician	Dose Adjustment	287 (25,9%)
	Request for suspension of the drug	141 (12,7%)
	Venous Thromboembolism Protocol (VTE)	74 (6,7%)
	Substitution with safer, more effective, cost-effective, available medication	68 (6,1%)
	Therapeutic duplicity	33 (3%)
	Request for Insertion of Non-Prescribed Medication	25 (2,3%)
	Medication Reconciliation	22 (2%)
	Dose Interval Change	14 (1,3%)
	Sedation and Analgesia	14 (1,3%)
	Suggested initiation of drug therapy	8 (0,7%)
	Medication via probe	6 (0,5%)
	Patients allergic to prescription drugs	6 (0,5%)
	Related to Parenteral Nutrition (PNT)	4 (0,4%)

(Continues on the next page.)

TABLE I - Classifications and quantities of pharmaceutical interventions performed in the study sectors

	Types of pharmaceutical interventions	Amount
Prescription adjustment interventions	Dilution Adjustment (Volume/Diluent)	209 (18,9%)
	Scheduling (Administration hours)	56 (5,1%)
	Volume Adjustment (Water Restriction)	45 (4,1%)
	Infusion time	27 (2,4%)
	Typing error	20 (1,8%)
	Physicochemical Stability	19 (1,7%)
	Route of administration altered according to patient conditions	13 (1,2%)
	Drug x Drug Interaction	11 (1%)
	Inadequate route of administration	6 (0,5%)
Total number of pharmaceutical interventions performed		**1108 (100%)**

When comparing, ICU 01 and Ward 2B, the main pharmaceutical intervention performed, i.e., the "dose adjustment", it was possible to identify that it occurred in greater number in the ICU, comprising a total of 187 of the 287 interventions performed.

Although the months with the highest number of prescriptions reviewed were March, April, and May 2021, as mentioned earlier, only the month of April also obtained, in addition to the large number of prescriptions reviewed (1,408 prescriptions), a high number of interventions performed (98 interventions), with the ICU responsible for 61 of these 98 interventions.

The other two months with the highest number of pharmaceutical interventions performed were January 2021, with 125 interventions, followed by December 2020, with 114 interventions. Among the numerous pharmaceutical interventions carried out, it was observed that those that stand out are related to antimicrobials and also to renal function, as shown in Figure 1.

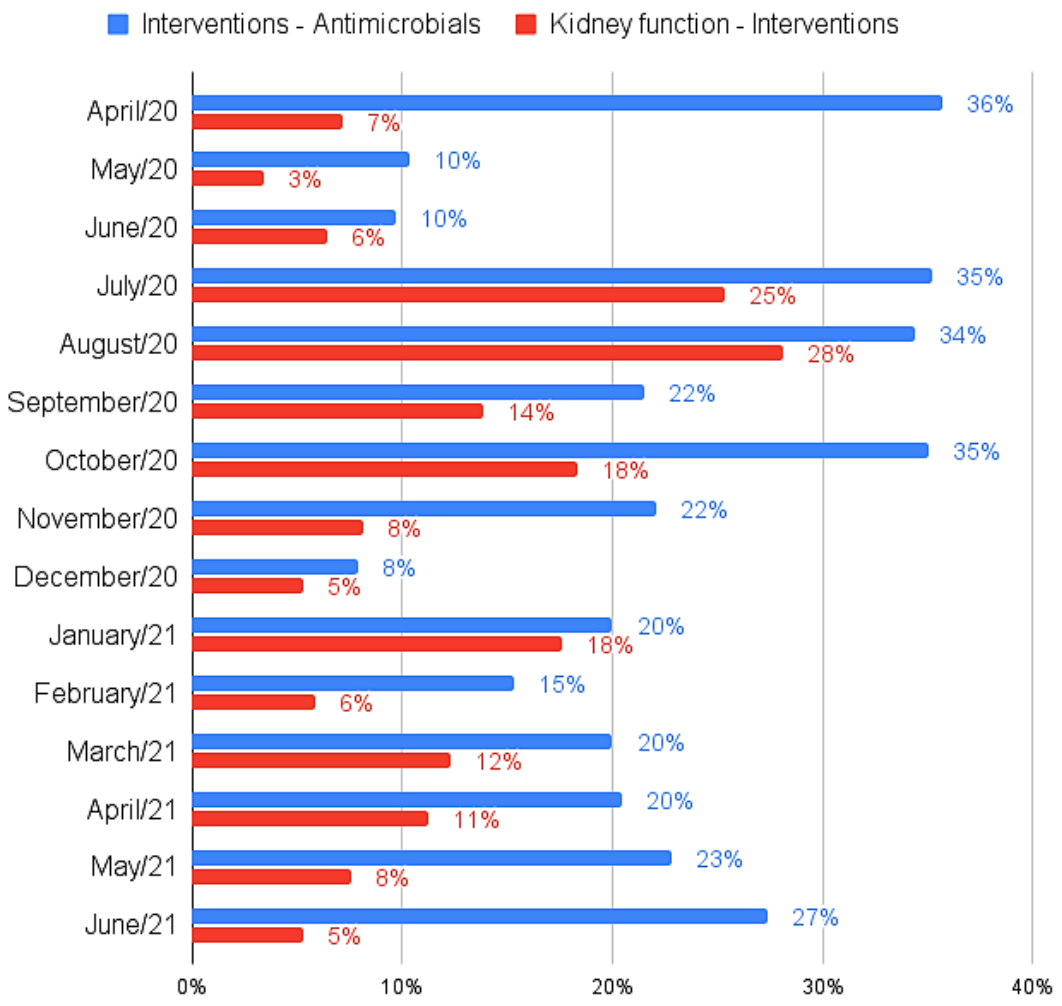

FIGURE 1 – Percentage of pharmaceutical interventions related to antimicrobials and related to renal function.

The blue lines in the figure are responsible for identifying the interventions related to antimicrobials, in which the months with greater realization of these interventions, were linked to the year 2020, being, the month of April responsible for 36%, followed by July and October, tied with 35%.

In this study, as will be discussed later, the interventions performed on antimicrobials, are due to dose adjustment with 61.6% of all interventions performed, and of these, 41.5% are due to renal function.

The interventions related to the patients' kidney function, identified by the red lines in the same figure, it is possible to verify that just like the interventions about the use of antimicrobials, the main months were also found in the year 2020, being: August with 28% of the interventions, followed by July with 25% and October with 18% of the interventions. Among the main classes of drugs that required renal function monitoring and adjustments are antimicrobials and low molecular weight heparin, such as Enoxaparin.

From this, it was sought to better understand the numerous pharmaceutical interventions related to antimicrobials, due to be the pharmaceutical class with the largest number of interventions performed, opting to classify each one of them in detail.

As can be seen in the Table II, the highest frequency of interventions regarding the use of antimicrobials occurred through dose adjustment in general, which

includes: "Dose adjustment (renal function)" with 41.5% (blue slice), "Dose adjustment (levels of vancomycin)" with 4.8% (orange slice) and "Dose adjustment" with 15.3% (red slice).

This last classification was left for all adjustments that came neither from renal function nor from levels of vancomycin. Together, all these forms of dose adjustment add up to 61.6% of all interventions performed due to antimicrobial use.

TABLE II - Classification of pharmaceutical interventions related to antimicrobials in the two sectors studied

	Types of pharmaceutical interventions related to antimicrobials	**Amount**
ICU No. 01 and in the hospitalization sector 2B	Dose Adjustment	45 (15,3%)
	Dose Adjustment (Renal function)	122 (41,5%)
	Dose Adjustment (Vancokinemia)	14 (4,8%)
	Dilution Adjustment (Volume/Diluent)	13 (4,4%)
	Infusion time	10 (3,4%)
	Patients allergic to prescription drugs	2 (0,7%)
	Physicochemical Stability	3 (1%)
	Request for Insertion of Non-Prescribed Medication	11 (3,7%)
	Request for suspension of the drug	32 (10,9%)
	Route of administration altered according to patient conditions	1 (0,3%)
	Scheduling (Administration hours)	10 (3,4%)
	Substitution with safer, more effective, cost-effective, available medication	15 (5,1%)
	Typing error	5 (1,7%)
	Volume Adjustment (Water Restriction)	11 (3,7%)
Total number of pharmaceutical interventions performed in the antimicrobials		**294 (100%)**

Both antimicrobial-related interventions and those due to renal function occurred more frequently in critically ill patients, i.e., in the ICU during the months of the study, with the exception of only the month of September 2020, in which, both interventions were greater in Inpatient Sector 2B.

Finalizing the results, now not only those focused on pharmaceutical care, but also encompassing pharmaceutical assistance in the use of medications, we detail, through Table III below, the medications of the antimicrobial class that were most involved in the interventions performed in each sector.

TABLE III - Antimicrobials present in the pharmaceutical interventions performed in ICU No. 01 and hospitalization sector 2B

Medication	Frequency	
	ICU No. 01	**Hospitalization sector 2B**
Amikacin	6 (2,7%)	1 (1,5%)
Amphotericin B	1 (0,4%)	0
Ampicillin + Sulbactam	5 (2,2%)	15 (22,1%)
Azithromycin	0	16 (23,5%)
Aztreonam	2 (0,9%)	0
Cefepime	9 (4,0%)	1 (1,5%)
Ceftazidime	8 (3,5%)	0
Ceftazidime + Avibactam	3 (1,3%)	0
Ceftriaxone	0	1 (1,5%)
Ciprofloxacin	0	1 (1,5%)
Clarithromycin	0	1 (1,5%)
Daptomycin	5 (2,2%)	0
Ertapenem	1 (0,4%)	0
Fluconazole	2 (0,9%)	0
Ganciclovir	7 (3,1%)	2 (2,9%)
Levofloxacin	8 (3,5%)	0
Meropenem	42 (18,6%)	9 (13,2%)
Metronidazole	4 (1,8%)	1 (1,5%)
Micafungin	2 (0,9%)	0
Oxacillin	2 (0,9%)	0
Piperacillin + Tazobactam	14 (6,2%)	15 (22,1%)
Polymyxin B	19 (8,4%)	0
Sulfamethoxazole +Trimethoprim	10 (4,4%)	1 (1,5%)
Teicoplanin	54 (23,9%)	2 (2,9%)
Tenofovir + Lamivudine	1 (0,4%)	0
Vancomycin	19 (8,4%)	2 (2,9%)
Voriconazole	2 (0,9%)	0
Total number	**226 (100%)**	**68 (100%)**

When comparing the antimicrobial profiles of the two sectors studied, the hospitalization sector 2B shown in Table III, that Azithromycin was only used in the ward, and reached 23.5% of the interventions that took place from April to August 2020. It is highlighted here the main pharmaceutical intervention related to Azithromycin: "Replacement with the safest, most effective, cost-effective medication available", with 14.7%.

In the ICU, according to Table III above, the profile of antimicrobials differs from inpatient Sector 2B, being the

most reported classes in pharmaceutical interventions the glycopeptides (Teicoplanin with 23.9% and Vancomycin with 8.4%), followed by the carbapenem Meropenem (18.6%) and the polypeptide Polymyxin B (8.4%).

DISCUSSION

Regarding the number of revised prescriptions and their acceptance rate, a study conducted for 12 months in a 200-bed hospital in São Paulo, reached a similar result to the one found in this study, with a 99.65% acceptance rate in the interventions performed from 78,341 revised prescriptions (Cardinal, Fernandes, 2014). Another study conducted in 2017, also had its acceptance rate estimated at 96.24% (Araujo *et al*., 2017). A good performance with the medical team can be closely related to the recognition of the work done by the Pharmacy Service (Cardinal, Fernandes, 2014).

During the pandemic period, pharmacists worked energetically to circumvent the drug shortage and also to adjust and create institutional protocols (Martins *et al*., 2020).

And it is in this context that the of the medical prescription gains greater importance, because when carried out by pharmacists, through a detailed revision, both in its technical and clinical aspects, that possible problems related to medicines, can be identified and corrected before dispensing and using them, continuing to promote the rational, safe and effective use of medicines. This analysis is necessary in all hospitalized patients (Cardinal, Fernandes, 2014; Carvalho, 2017; Brazilian Society of Hospital Pharmacy, 2017).

As for the number of prescriptions reviewed, no studies with similar values were found. It is believed that this result may be linked to the fact that the first months of 2021 had a high number of cases of COVID-19 in the region, presenting only small oscillations in the second four months and a considerable drop only after the third four according to the Annual Management Report (AMR) of the municipality of Joinville (Joinville, 2022).

Collaborating with this perspective are the data from the "COVID-19 Joinville Panel" which, since its creation on March 18, 2020, by information collected and published daily by the Secretary of Health (SES) and the Secretary of Communication (SECOM), showed the number of inpatients, both in the ward and in the ICU. In the months in question (March, April, and May 2021), the month of March, considering both the ICU and the ward, had an average of 271 occupancies/day, the month of April, 299 occupancies/day, and the month of May, 260 occupancies/day. Furthermore, March had the highest occupancy in the ward among the three months, with an average of 143 occupancies/day, and April had the highest number of occupancies in the ICU, with an average of 178 occupancies/day. Finally, in 2021, the month of April was considered the most critical of the year due to the pandemic by COVID-19 (Joinville, 2023).

With regard to the pharmacist's autonomy in carrying out their activities, it can be said that, according to Art. 4 of the menu that regulates the clinical attributions of the pharmacist, that he must carry out his activities with autonomy, based on bioethical values and professional principles (Brazil, 2013). In this sense, although the results are optimistic regarding the pharmacist work provided at the study site, no other studies were found that discuss interventions that are of the professional's autonomy.

At the study site, a "Pharmaceutical Services Policy" was instituted, in which there are agreements between the medical team and the Pharmacy Sector for the characterization and performance of interventions considered to be the pharmacist's autonomy (Unimed Joinville Hospital Center, 2021).

That way, the performance of this professional will be based on the search for quality, safety and efficacy of the pharmacological treatment of their patients and thus create possibilities for a good performance with the health team, so, in recognition of the work done (Cardinal, Fernandes, 2014; Rêgo, Comarella, 2015).

The pharmaceutical intervention "Dose adjustment" was the most performed intervention in this study, and it is important to mention that this is linked to the use of antimicrobials and the renal function of critically ill patients, which will be discussed in more detail below. As for the other two most reported interventions, these were: "Adjustment in dilution (Volume/Diluent)" and "Request for discontinuation of medication", both were more reported in hospitalization sector 2B, and here, it can already be emphasized

that, in their majority, they are due to the use of the glucocorticoid Dexamethasone.

After the publication of the RECOVERY study in The New England Journal of Medicine, which indicated the use of this drug for the treatment of COVID-19, given the results of the effectiveness of the drug in mediating the inflammatory lung injury caused by the virus, and thus slowing the evolution to a more severe condition, respiratory failure and death, the use of this drug was adopted by the local study, especially in the inpatient sector (Horby *et al*., 2021).

The recommendation for use was 6 mg (without weight adjustment) per day, for 10 days, and intravenous administration was preferred. Later, this recommendation was also reaffirmed by *Comissão Nacional de Incorporação de Tecnologias no Sistema* Único *de Saúde - CONITEC*, (CONITEC - National Commission for the Incorporation of Technologies in the Unified Health System), in its clinical protocol and therapeutic guideline, published in 2021 (Brazil, 2021).

In view of the use of this glucocorticoid for this indication, it was established, at the request of the medical clinic, that the drug in question be diluted in 50 milliliters of 0.9% saline solution and performed in 30 minutes of intravenous infusion, to avoid possible adverse effects. This dilution profile is compatible with that indicated by literature (Trissel, 2015).

As this was not yet an usual dilution at the site and adopted mainly for patients with a dose of 6mg/day, with a direct indication for COVID-19, in many cases it was necessary for the pharmacist to adjust the dilution manually, which contributes to one of the most performed interventions being the "Adjustment in dilution (Volume/Diluent)" in Inpatient Ward 2B. The "Request for medication suspension", as far o it is concerned, was also, in most cases, related to the use of the same glucocorticoid, as the treatment time recommended by the protocol was carefully controlled by the pharmacy.

Therefore, the interventions resulting from this medicine contributed mainly to pharmacoeconomics, when considering the reduction of treatment/day, through the request to suspend its use while following and controlling the days of use, according to the internationally suggested protocol, with approval from *CONITEC* (Oliveira *et al*., 2023).

As mentioned in the results, among the months with the highest number of prescriptions reviewed (March, April and May 2021), only the month of April also had a high number of pharmaceutical interventions, with 98 interventions performed from 1,408 prescriptions reviewed. Of these, 61 interventions were performed in ICU patients. Which brings us once again to the fact that the month of April, was considered the most critical in relation to the disease in the year 2021 in the region (Joinville, 2022). Finally, not necessarily the months with the highest number of revised prescriptions are the same with a high number of interventions.

About interventions regarding the use of antimicrobials, a study published in 2021, also about pharmaceutical interventions, but this one, only in the ICUs of a university hospital, showed that of the 1,145 interventions performed, 364 (31.8%), were related to the use of antimicrobials (Lima *et al*., 2021).

Regarding the treatment with antimicrobials, although it is established that they are ineffective against the SARS-CoV-2 virus, which causes COVID-19, there is the suggestion of empirical treatment for patients with respiratory failure or on mechanical ventilation. CONITEC also does not recommend the use of antimicrobials without suspicion of associated bacterial infection, and in its considerations maintains that there is no basis for the routine use of antimicrobials. However, patients who, on admission, have a possible infectious focus, such as a pulmonary radiological consolidation, should receive antimicrobials empirically based on clinical judgment. The team should also keep an eye out for suspected infections such as Mechanical Ventilator-Associated Pneumonia (VAP) (Brazil, 2021).

VAP is a type of Healthcare Associated Infection (HAI), resulting in a serious public health problem in developing countries, such as Brazil. It is very common in critically ill patients and those with prolonged time on mechanical ventilation, because with the health emergency caused by the COVID-19 pandemic, there was a great need for the use of these respirators, resulting in a 300% increase in VAP cases in 2020 compared to 2018 (Fortaleza *et al*., 2017; Pasetti *et al*., 2022).

Associação de Medicina Intensiva Brasileira – AMIB (AMIB - Brazilian Association of Intensive Care Medicine - AMIB), in conjunction with the Brazilian Society of Infectology and the Brazilian Society of Pneumology and Tisiology, also considered, that if these infections occur, antimicrobial use should be initiated in a similar way as for other patients without COVID-19, but considering the epidemiology and local protocols (Falavigna *et al*., 2020). However, the use of antimicrobials, especially broad-spectrum ones, always raises alarm bells due to microbial resistance, which is a public health challenge (Oliveira *et al*., 2023).

It is not yet possible to measure the size of the impact that the pandemic due to COVID-19 has caused with regard to antimicrobial resistance worldwide, as studies are still being published (Rawson *et al*., 2020). And according to an integrative review carried out by Oliveira *et al*. (2023), even after almost 4 years of the beginning of the pandemic and almost 1 year of the end of this health emergency worldwide, studies in the area of the use of antimicrobials, even more so, those focused on the role of the pharmacist in promoting their use rational, are scarce, leaving a gap in current information.

However, a review article discussed that, of the 2,010 patients mentioned, 1,450 (72%) used antimicrobials, many of which were broad-spectrum, in addition to having been used both in the wards and in critical units (Rawson *et al*., 2020).

As mentioned, although it is not possible to measure data regarding antimicrobial resistance, we know that when antimicrobials are used incorrectly, that is, for an inadequate time or doses, the possibility of adverse effects is significantly higher (Bruniera *et al*., 2015). Nephrotoxicity, an example of a common adverse effect in hospitalized patients, is a result of the use of several drugs and possible associated comorbidities associated (Mas-Font *et al*., 2017; Mercado, Smith, Guard, 2019).

The interventions related to the patients' renal function are remarkable in patients with COVID-19, because COVID-19 is a disease that is not only limited to respiratory tract damage, but also presents numerous complications in other organs, such as the kidneys, causing kidney damage, which in an acute form is a condition inherent to the complications arising from this disease (Carvalho, Paula, Peixoto, 2021; Duarte *et al*., 2020). Furthermore, the use of vasoactive drugs and even the use of mechanical ventilation are considered nephrotoxic factors, and precisely because of this, this is a condition so present in ICUs (Mas-Font *et al*., 2017; Mercado, Smith, Guard, 2019).

No studies were found that discuss only the dose adjustment in the class of antimicrobials, but considering Table I, it is observed that the percentage of the "Dose Adjustment" intervention, in this case, related to all drugs, and not only to antimicrobials, was 25.9% (287 of 1,108 interventions). And from this, one finds results in the literature of 12.1% (Silva, Pimentel, Teixeira, 2022) and 12.2% (Lima *et al*., 2021)

Close to the results found in this study, there is a study conducted in a tertiary hospital, which made two distinct collections, being, one collection without the clinical service focused on the review of prescription drugs (period A) and another collection after the implementation of the service (period B). The results related to dose adjustment, in period A was was 25% and in period B, 35%.

However, it is important to note that if kidney function alone accounted for more than 41% of all interventions, back to the step, that Acute Kidney Injury (AKI) is a condition that affects a significant number of patients, as one of the main complications arising from COVID-19 (Farias *et al*., 2016). Thus, many antimicrobials needed to have their doses adjusted according to renal function, because this is one way to prevent nephrotoxicity, or at least reduce renal fragility that the toxic effects of these drugs generate, in order to reduce the aggravation of renal of these drugs generate, in order to reduce the aggravation of the renal clinical picture of the patient and the consequent possibility of mortality (Ciraque, Silva, Silva, 2022).

Azithromycin, the most reported antibiotic in the interventions of hospitalization sector 2B, a broad-spectrum macrolide, showed in vitro evidence of inhibition of SARS-CoV-2 virus replication and also a virucidal effect (Furtado *et al*., 2020). Due to this and the lack of a specific drug therapy, Azithromycin was used at the beginning of the pandemic as an

alternative treatment (Tarighi *et al*., 2021). The interventions related to this antimicrobial are all dated in the year 2020, the same year that evidence from studies showed that it, when used in the standard care of patients affected with COVID-19, brought no significant clinical improvement (Furtado *et al*., 2020). AMIB, together with the Brazilian Society of Infectology and the Brazilian Society of Pulmonology and Phthisiology, also recommended against the use of this drug (Falavigna *et al*., 2020).

The main pharmaceutical intervention on Azithromycin was "Substitution with safer, more effective, cost-effective, available medication". Which was due to the substitution of the injectable pharmaceutical form for the oral one for a better stock management, linked to a temporary shortage of the injectable presentation in the region, because Azithromycin was one of the most widely used drugs at the hospital level at the beginning of the pandemic (Martins *et al*., 2020).

As for the most reported antibiotics in the ICU (Teicoplanin, Vancomycin, Meropenem and Polymyxin B), according to a study carried out in 2022, Meropenem, with 22.5% and Polymyxin B with 12.6%, were the most prescribed antibiotics in the COVID ICU and the most registered infectious focus in this unit, as expected, it was pulmonary, occupying 76.6% of the total results. Also, regarding the use of antibiotics, the same study mentions that 79% of the patients were using combination therapy, with 2 to 5 antibiotics (Lima *et al*., 2022).

It was verified through The Sanford Guide that of the 3 most reported antibiotics (Teicoplanin, Meropenem and Polymyxin B), only Polymyxin B does not have adjustments due to renal function, despite requiring monitoring. Meropenem and teicoplanin, on the other hand, have specific adjustments according to creatinine clearance (Gilbert *et al*., 2022). This corroborates with the results of dose adjustment interventions, where 41.5% were due to renal function, since, as already widely discussed in this work, patients with COVID-19, due to multifactorial issues, end up developing kidney damage, as a condition inherent to the disease (Duarte *et al*., 2020).

The use of broad-spectrum antimicrobials in patients affected by COVID-19 in its severe form was global. Given this situation, patients can be at high risk when using medicines and the clinical pharmacist is an important professional to collaborate in optimizing pharmacotherapy, in addition to being an indispensable professional in managing the use of antimicrobials in an adequate and safe way (Martins *et al*., 2020).

Finally, regarding the general performance of this professional through the detailed review of the pharmacotherapy performed, it is possible to observe, although without detailed measurement of all classes of drugs involved, that some examples of interventions such as "Dose adjustment", "Request for suspension of the drug", and "Infusion time", among others shown in Table I, contributed to the reduction of adverse effects.

When there are inadequate doses or prolongation of the treatment time, the appearance of adverse effects increases (Bruniera *et al*., 2015).

Vancomycin, one of the glycopeptides most involved in the interventions carried out, when used incorrectly, whether through inadequate doses or prolonged treatment, increases the chances of the appearance of unwanted adverse effects, which, together with risk factors inherent to the criticality of the elderly patients hospitalized in ICUs, it is nephrotoxic and can cause AKI (Mas-Font *et al*., 2017; Mercado, Smith, Guard, 2019).

In short, the vast majority of interventions were made in the use of the glucocorticoid Dexamethasone and in the use of the antimicrobials Azithromycin, Meropenem, Polymyxin B, Teicoplanin and Vancomycin. In this way, we can point out that, for the most part, the pharmacists' interventions possibly resulted in pharmacoeconomics, because when requests were made to discontinue the drugs Dexamethasone and Azithromycin, their treatment/day was reduced, not to mention issues such as length of hospital stay and costs of medical and hospital materials. As for the antimicrobials Meropenem, Vancomycin and Teicoplanin, dose adjustment interventions due to renal function have brought benefits such as identifying possible therapeutic failures, minimizing adverse effects such as nephrotoxicity or at least reducing renal fragility to the toxic effects of the drugs (Ciraque, Silva, Silva, 2022; Santos *et al*., 2019).

CONCLUSION

Although this study had some limitations, such as being carried out in a single medical center, the number of prescriptions reviewed and the pharmaceutical interventions resulting from these reviews proved to be significant, since they contributed to ensuring the effectiveness and safe care of infected patients, through the optimization of pharmacotherapy carried out by pharmacists. In addition, as this is a global health emergency scenario due to COVID-19, the need for clinical services provided by pharmacists to be maintained was evident, as this professional was present with the health team, in the development of guidelines and also in the management of pharmacological treatments, following the rapid change and evolution of information about the use of medicines, thus guaranteeing their safe, rational and effective use.

ACKNOWLEDGMENT

I thank all the pharmacists at the study site, who, although they were not the authors of this study, were also responsible for all the results achieved due to their actions during the COVID-19 pandemic.

REFERENCES

Al-Quteimat OM, Amer AM. SARS-CoV-2 outbreak: How can pharmacists help? Res Social Adm Pharm. 2020;17:480-482.

Araujo EO, Viapiana M, Domingues EAM, Oliveira GS, Polisel CG. Pharmaceutical interventions in an intensive care unit at a university hospital. Rev Bras Farm Hosp Serv Saude. 2017;8:25-30.

Brazil. Federal Pharmacy Council. Resolution no. 585, of August 29, 2013. Amendment: Regulates the clinical attributions of pharmacists and makes other provisions [*S. l.*], 11p. 29 Aug. 2013.

Brazil. Ministry of Health. Recommendation report: Clinical Protocols and Therapeutic Guidelines: Brazilian Guidelines for Hospital Treatment of Patients with COVID-19 - Chapter 2: Drug Treatment. CONITEC. Brasilia (DF), n. 638, 111p., 2021.

Brazilian Society of Hospital Pharmacy, compiler. Minimum Standards for Hospital Pharmacy. 3ed. São Paulo: 2017. 40 p.

Bruniera FR, Ferreira FM, Saviolli LRM, Bacci MR, Feder D, Pedreira MLG. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci. 2015;19:694-700.

Cardinal LSM, Fernandes CS. Pharmaceutical intervention in the prescription validation process. Rev Bras Farm Hosp Serv Saude. 2014;5:14-19.

Carvalho DCMF. Clinical Pharmacy and Patient Care Manual [bibliography]. 1ed. Rio de Janeiro: Atheneu; 2017. 303 p.

Carvalho LF, Paula TCGQ, Peixoto VS. Acute kidney injury in patients diagnosed with COVID-19 in an ICU in southwestern Goiás. RSD. 2021;10:1-9.

Ciraque A, Silva CCS, Silva AS. Drug-induced nephrotoxicity. Rev Terra & Cult, 2022.38:35-51.

Duarte PMA, Filho FAGB, Duarte JVA, Duarte BA, Duarte IA, Lemes RPG, et al. Application of the FASTHUG-MAIDENS mnemonic and evaluation of its impact on pharmaceutical interventions in an adult intensive care unit. Rev Assoc Med Bras. 2020;10(66):1335-1337.

Falavigna M, Colpani V, Stein C, Azevedo LCP, Bagattini AM, Brito GV, et al. Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology. Rev Bras Ter Intensiva. 2020;32:166-196.

Farias TF, Aguiar KS, Rotta I, Belletti KMS, Carlotto J. Implementation of a clinical pharmaceutical service in hematology. Einstein. 2016;14:384-390.

Fortaleza CMCB, Padoveze MC, Kiffer CRV, Barth AL, Carneiro ICRS, Giamberardino H I G, et al. Multi-state survey of healthcare-associated infections in acute care hospitals in Brazil. J Hosp Infect. 2017;96:139-144.

Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet. 2020;396:959–967.

Gilbert DN, Chambers HF, Saag MS, Pavia AT, Boucher HW, Black D, et al. The Sanford Guide: To Antimicrobial Therapy.52th ed. Sperryville, Virginia: INC; 2022. 341 p. ISBN: 978-1-944272-20-3.

Hatah E, Braund R, Tordoff J, Duffull S B. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. BJCP. 2013;77:102-115.

Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384:693-704.

Hua X, Gu M, Zeng F, Hu H, Zhou T, Zhang Y, et al. Pharmacy administration and pharmaceutical care practice

in a module hospital during the COVID-19 epidemic. J Am Pharm Assoc.2020;60:431-438.

Joinville. Annual Management Report (RAG) 2021. Strategic management and articulation of the network [Internet]. 2022. [cited 2023 Jan 31]; Available from: https://www.joinville.sc.gov.br/publicacoes/relatorios-anuais-de-gestao-em-saude-do-municipio-de-joinville/

Joinville. Secretariat of Health (SES) and Secretariat of Communication (SECOM). COVID-19 cases in Joinville (COVID-19 Panel) [Internet]. 2023. [cited 2023 Jan 31]; Available from: https://www.joinville.sc.gov.br/publicacoes/relatorios-anuais-de-gestao-em-saude-do-municipio-de-joinville/

Lima B S S, Gomes A C R, Santos M E A, Gripp M R, Lima V P. Results of the profile of antibiotic use in covid intensive care units, non-covid intensive care units and covid wards using the prevalence point analysis method during 2020. Braz J Infect Dis. 2022;26.

Lima Í M, Vidigal S B, Lima N M, Carvalho D A, Santos E J, Junior A C, et al. Application of the FASTHUG-MAIDENS mnemonic and evaluation of its impact on pharmaceutical interventions in an adult intensive care unit. Rev Bras Farm Hosp Serv Saude.2021;12:1-9.

Lynch M, O'Leary A C. COVID-19 related regulatory change for pharmacists - The case for its retention post the pandemic. Res Social Adm Pharm. 2020;17:1913-1919.

Mallhi TH, Liaqat A, Abid A, Khane YH, Alotaibi, Nasser H, Alzarea AI, et al. Multilevel Engagements of Pharmacists During the COVID-19 Pandemic: Front Public Health.2020;8:1-14.

Martins MAP, Medeiros AFA, Almeida CDC, Reis AMM. Preparedness of pharmacists to respond to the emergency of the COVID-19 pandemic in Brazil: a comprehensive overview. Drugs Ther Perspect.2020;36:455-462.

Mas-Font S, Ros-Martinez J, Pérez-Calvo C, Villa-Díaz P, Aldunate-Calvo S, Moreno-Clari E, et al. Prevention of acute kidney injury in Intensive Care Units. Med. Intensiva. 2017;41:116-126.

Mercado MG, Smith DK, Guard EL. Acute Kidney Injury: Diagnosis and Management. Am Fam Physician.2019;100:687-694.

Oliveira SJV, Santiago MAA, Lisboa LFT, Grisólia DPA, Costa CMM, Grisólia ABA. The role of pharmacists in promoting the rational use of antibiotics in hospital settings: An integrative review. Research, Society and Development [Internet]. 2023 [cited 2024 Jan 2];12 DOI 0.33448/rsd-v12i11.43608. Available from: https://rsdjournal.org/index.php/rsd/article/view/43608

Pasetti ES, Caiana ABS, Ribeiro KO, Freitas EL, Gomes ECS, Pereira LGS, et al. Etiology and antimicrobial sensitivity profile of ventilator-associated pneumonia (VAP) during the covid-19 pandemic in a hospital in the greater abc paulista region. Braz J Infect Dis.2022;26:1.

Pharmaceutical Care Network Europe. Classification for drug related problem [Internet]. 2019 [cited 2024 Jan 3]; 9. Available from: https://www.pcne.org/upload/files/334_PCNE_classification_V9-0.pdf

Rahn B, Zonzini FH, Mendes AM. Review of in-hospital pharmacotherapy: risk and network analysis. Rev Bras Farm Hosp Serv Saude [Internet]. 2023 [cited 2024 Jan 3];14 DOI 10.30968/rbfhss.2023.144.0995. Available from: https://rbfhss.org.br/sbrafh

Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis.2020;71:2459–2468.

Rêgo MM, Comarella L. The role of pharmaceutical analysis of hospital prescriptions. Caderno Saúde e Desenvolvimento. 2015.7:17-31.

Santos KC, Barbosa, MJ, Araújo WNMS, Sena VV, Souza T. The Role of Clinical and Hospital Pharmacy in Managing the Use of Antimicrobials in a Public Hospital in the Federal District. Revista de Divulgação Científica Sena Aires.2019;8(2):153-159.

Silva JG, Pimentel AF, Teixeira CA. Analysis of pharmaceutical interventions in a COVID-19 intensive care unit at a university hospital in Rio de Janeiro. Rev Bras Farm Hosp Serv Saude.2022;13:1-9.

Tarighi P, Eftekhari S, Chizari M, Sabernavaei M, Jafari D, Mirzabeigi P. A review of potential suggested drugs for coronavirus disease (COVID-19) treatment. Eur J Pharmacol. 2021;895. DOI 10.1016/j.ejphar.2021.173890. Available from: https://pubmed.ncbi.nlm.nih.gov/33482181/

Trissel L. A. Handbook on Injetable. Drugs. 18º ed. Bethesda: American Society of Health – System Pharmacists; 2015.

Unimed Joinville Hospital Center. Pharmaceutical Assistance Policy. 39062th ed. Joinville: [publisher unknown]; 2021. 1-15 p. 2.00 vol.

Visacri MB, Figueiredo IV, Lima TM. Role of pharmacist during the COVID-19 pandemic: A scoping review. Res Social Adm Pharm.2021;17:1799-1806.

Received for publication on 01st September 2023
Accepted for publication on 22nd January 2024