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Analysis of pharmaceutical interventions in a COVID-19 intensive care unit of a university hospital in Rio de Janeiro

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Abstract

Objectives. To evaluate data from pharmaceutical interventions performed in an intensive care unit (ICU) dedicated to COVID-19. **Methods.** A retrospective cross-sectional study was carried out in an ICU dedicated to COVID-19 of a university hospital in Rio de Janeiro, during the period from january to june of 2021. Data was obtained from pharmaceutical interventions recorded in pharmacotherapeutic follow-up forms, carried out by a team of clinical and resident pharmacists, based on on-site work with the multidisciplinary team. The daily review of pharmacotherapy and clinical assessment of patients was based on an adaptation of the FASTHUG-MAIDENS mnemonic, and the interventions performed were compiled in an online Google Drive spreadsheet. The identified drug-related problems were categorized according to the types of medication errors involved, and the cited drugs were classified according to the Anatomical Therapeutic Chemical Code (ATC). Forms that did not contain registered interventions were excluded from the analysis. **Results.** A total of 223 patients were followed, and 1,140 pharmaceutical interventions were performed, with an average of 5.1 interventions per patient and an acceptance rate of 85.2%. Among the medication-related problems, categorized as medication errors, those with the highest frequency of interventions were omissions of doses or medications (357), inadequate prescriptions (169), and incorrect doses (168). Among the drug classes most involved in interventions, digestive system and metabolism (243) and nervous system (221) had the highest number of recorded recommendations. Regarding the other types of medication errors recorded (161), 91 interventions were related to stockouts and variability in stock, as a reflection of drug shortages caused by COVID-19. **Conclusion.** The pharmacist, as part of the multidisciplinary team, optimizes the pharmacotherapeutic follow-up and helps in the identification and prevention of drug-related problems. The data obtained point out specific pharmacotherapeutic issues that need more attention during the monitoring carried out in the observed scenario and can guide the formulation of actions aimed at patient safety and protocols aimed at the use of medicines.

Keywords: COVID-19, intensive care, pharmaceutical interventions, clinical pharmacist.

Análise das intervenções farmacêuticas em unidade de terapia intensiva COVID-19

Resumo

Objetivo. Avaliar os dados das intervenções farmacêuticas realizadas em uma unidade de terapia intensiva (UTI) dedicada a COVID-19. **Metodologia**. Estudo transversal retrospectivo, realizado em UTI dedicada a COVID-19 de um hospital universitário no Rio de Janeiro, durante o período de janeiro a junho de 2021. Foram analisados dados obtidos de intervenções farmacêuticas registradas em formulários de acompanhamento farmacoterapêutico, realizado por uma equipe de farmacêuticos clínicos e residentes, a partir da atuação *in loco* junto à equipe multiprofissional. A revisão diária da farmacoterapia e avaliação clínica dos pacientes, foi baseada na adaptação do mnemônico FASTHUG-MAIDENS, e as intervenções realizadas compiladas em planilha online do Google Drive. Os problemas relacionados a medicamentos identificados foram categorizados conforme os tipos de erros de medicação envolvidos, e os medicamentos citados classificados segundo o Anatomical Therapeutic Chemical Code (ATC). Foram excluídos da análise os formulários que não continham intervenções registradas. **Resultados.** Foram acompanhados 223 pacientes, sendo realizadas 1.140 intervenções farmacêuticas, com média de 5,1 intervenções por paciente e taxa de aceitação de 85,2%. Entre os problemas relacionados à medicamentos, categorizados como erros de medicação, os que apresentaram maior frequência de intervenções foram omissões de doses ou medicamentos (357), prescrições inadequadas (169) e doses incorretas (168). Entre as classes de medicamentos mais frequentemente envolvidas nas intervenções, aparelho digestivo e metabolismo (243) e sistema nervoso (221) obtiveram o maior número de recomendações registradas. Em relação aos outros tipos de erros de medicação registrados (161), 91 intervenções foram relacionadas à rupturas e variabilidade no estoque, como reflexo do desabastecimento de medicamentos causado pela COVID-19. **Conclusão.** O farmacêutico, enquanto parte da equipe multiprofissional, otimiza o acompanhamento farmacoterapêutico e auxilia na identificação e prevenção de problemas relacionados aos medicamentos. Os dados obtidos, apontam questões farmacoterapêuticas específicas que necessitam de maior atenção durante o acompanhamento realizado no cenário observado, e podem orientar a formulação de ações voltadas à segurança do paciente e protocolos voltados ao uso de medicamentos.

Palavras-chave: COVID-19, terapia intensiva, intervenções farmacêuticas, serviço de farmácia clínica.

Introduction

In 2019, the city of Wuhan, China, gained worldwide prominence by becoming the epicenter of a severe respiratory syndrome caused by a new betacoronavirus (SARS-CoV-2) and called "Coronavirus disease 2019" or COVID-19[1]. In March 2020, the significant number of cases and global spread lead the World Health Organization (WHO) to decree the onset of a new pandemic[1].

In Brazil, the Ministry of Health (*Ministério da Saúde*, MS) announced the first COVID-19 case on February 26th and the first death was recorded on March 17th, 2020. Due to their heterogeneity, the symptoms caused by COVID-19 can range from mild clinical manifestations such as cough, fatigue and fever to respiratory and systemic complications, leading to hospitalization and admission to intensive care units[2]. Certain characteristics such as advanced age, male gender and presence of comorbidities were associated to worse prognoses and to development of the most severe form of the infection[3]. Evaluations of recent studies on the clinical profile of these patients showed that, among the most common disorders presented, were occurrence of thromboembolic events, severe hypoxemic respiratory failure and acute renal failure; in addition to development of associated bacterial infections and liver dysfunction[4-5].

The need for ventilatory support and the use of multiple potentially dangerous drugs reflected the severity of the condition presented by these patients, constituting important risk factors related to hospitalization and the safe pharmacotherapy management[6]. In this scenario, the pharmaceutical industry is not only devoted to providing technical support to other professionals, but also to evaluation and pharmacotherapy follow-up aiming at the best clinical results and at patient safety[7-8].

Thus, the objective of this study was to quantify and characterize the pharmaceutical interventions performed during the pharmacotherapy follow-up of patients hospitalized in an exclusive COVID-19 intensive care unit and to discuss its possible clinical contributions.

Methods

This is a retrospective cross-sectional study carried out from January 1st to June 30th, 2021, in an exclusive COVID-19 intensive care unit of a university hospital from Rio de Janeiro. Recognized for medium- and high-complexity care, the hospital was listed by the Ministry of Health and by State and Municipal Health Departments as one of the reference institutions for receiving COVID-19 cases[9]. For the care of the most severe cases, two intensive care units exclusively devoted to COVID-19 were made available, offering comprehensive and interdisciplinary assistance[10].

The team of pharmacists consisted of 6 clinical pharmacists with previous training in ICU and 1 resident pharmacist taking turns in shifts, working *in loco* with the interdisciplinary team during the day period, daily, including weekends and holidays, and with a minimum team comprised by 2 pharmacists. During the study period, the team carried out the pharmacotherapy follow-up, continuously and systematically, in 17 beds that made up one of the COVID-19 intensive care units.

A working method adapted from the FASTHUG-MAIDENS mnemonic rule[11] was used for the systematic pharmacotherapy review and daily evaluation of the data related to the management of issues such as dosage, indication and duration of the pharmacological treatments in general, drug interactions with potential clinical relevance, medication reconciliation and situations specifically related to analgesia, sedation, neuromuscular blockade in mechanical ventilation, thromboprophylaxis, pharmacological management of *delirium*, stress ulcer and corneal ulcer prophylaxis, use of prokinetics and laxatives, glycemic control, corticosteroid therapy and use of antimicrobials, among others with occurrence in intensive care[12].

The pharmaceutical interventions, an integral part of the pharmacotherapy follow-up process, were carried out through direct contact with the medical team during or after the daily interprofessional rounds. For the purposes of the study, a pharmaceutical intervention was considered to be any record in the pharmacotherapy follow-up form based on the identification of drug-related problems (DRPs) associated with medication errors (MEs) and/or observation of inadequacies in the pharmacotherapy regarding the medication or the patient's clinical condition at the time of the evaluation[13]. In a subsequent stage of the analysis, using the data from the medical records and the patients' prescriptions, the interventions considered accepted were those that resulted in concrete changes in the drug prescriptions.

The study was based on the analysis of the data obtained through the records made in pharmacotherapy follow-up forms, after excluding those that did not contain recorded interventions or that had filling-out failures that compromised the final evaluation. The data collected were the following: gender, date of birth, hospital and COVID-19 ICU admission dates, follow-up initiation date, outcome (discharge or death), and the interventions recorded. All the data were compiled in an online Google Drive spreadsheet and the interventions were categorized according to the study by Otero López et al[14], with adaptations, considering the intensive care scenario in a pandemic context, and the medications involved in the interventions were classified according to the Anatomical Therapeutic Chemical Code (ATC)[15].

Finally, the interventions were also classified according to their relationship with each of the FASTHUG-MAIDENS domains. It is noted that, for this classification, the same intervention can involve a medication related to more than one domain from the mnemonic rule. For example, enoxaparin, used for anticoagulation and prevention of thrombotic events, was the main drug involved in the interventions related to the different domains aimed at thromboprophylaxis and medication doses.

The research followed all the ethical precepts in force defined in CNS Resolution No. 466/12 of the National Health Council, being approved by the HUCFF Research Ethics Committee with CAAE No. 51268021.2.0000.5257 and favorable opinion No. 5,119,167.

Results

During the study period, 223 patients were monitored in the COVID-19 Intensive Care Unit. Of these, 26 did not present records of interventions or had incomplete records, which resulted in 197 (88.3%) patients with at least one intervention throughout their hospitalization. No significant discrepancy was detected between the number of male (50.6%) and female (49.3%) patients, with predominance of the age group between 60 and 79 years old (49.7%). The mean hospitalization time in the COVID-19 ICU was 14.2 days and 135 patients (60.5%) evolved to death during the period analyzed (Table 1).

Table 1. Profile of the patients monitored in the COVID-19 Intensive Care Unit (ICU) from January to June 2021.

Data analyzed	Descriptive statistics
Patients monitored	**n = 223 (100)**
Gender, n (%)	
Male	113 (50.6)
Female	110 (49.3)
Age group (years old), n (%)	
20-40	13 (5.8)
41-59	83 (37.2)
60-79	111 (49.8)
≥80	16 (7.2)
ICU hospitalization time (days), n (%)	
≤ 7	78 (35%)
8-14	66 (30%)
15-21	35 (16%)
22-30	21 (9%)
≥30	23 (10%)
Mean time in the ICU, n	14.2
Outcome, n (%)	
Hospital discharge	88 (39.5%)
Death	135 (60.5%)

A total of 1,140 pharmaceutical interventions based on the pharmacotherapy follow-up and daily review of the prescriptions were performed. A mean of 5.1 interventions were performed per patient, of which 190 (96.4%) had at least one change in their prescription after the intervention. The problems related to pharmacotherapy were categorized and, according to the highest frequencies of interventions, 357 (31.3%) dose or medication omissions, 169 (14.8%) inadequate prescriptions and 138 (12.1%) suggestions referring to incorrect doses were recorded (Table 2).

Table 2. Analysis of the pharmaceutical interventions performed and of the related medication errors during pharmacotherapy follow-up in a COVID-19 Intensive Care Unit (ICU) between January and June 2021.

Data obtained	Descriptive statistics
Interventions	
Total number of interventions performed, n (%)	1,140 (100)
Total number of accepted interventions, n (%)	845/1,140 (74.1)
Total number of patients with at least 1 intervention performed, n (%)	197/223 (88.3)
Number of patients with at least 1 accepted intervention, n (%)	190/197 (96.4)
Mean number of interventions performed per patient, n	5.1
Medication errors related to the interventions	
Dose or medication omission, n (%)	357/1,140 (31.3)
Inadequate prescription, n (%)	169/1,140 (14.8)
Incorrect dose, n (%)	138/1,140 (12.1)
Inadequate administration frequency, n (%)	138/1,140 (12.1)
Inadequate administration route, n (%)	84/1,140 (7.3)
Treatment length in time, n (%)	69/1,140 (6.0)
Presentation of the medication not available in the institution, n (%)	53/1,140 (4.6)
Item with critical stock, n (%)	20/1,140 (1.7)
Insufficient treatment monitoring, n (%)	19/1,140 (1.6)
Medication not available in the institution, n (%)	18/1,140 (1.6)
Other types, n (%)	75/1,140 (6.6)

Considering the therapeutic classes most frequently involved, 243 (21.3%) interventions were performed for medications that act on the digestive system and metabolism, 221 (19.3%) for drugs related to the nervous system, 199 (17.4%) for medications acting on the blood and hematopoietic organs, and 151 (13.2%) for general anti-infectives for systemic use. Present in the routine of the pharmacotherapy follow-up in intensive care units since 2019, the indication for corneal ulcer prophylaxis with use of methylcellulose-based eye drops turned this the medication into the one with the highest absolute frequency of records in interventions (133) (Table 3).

Table 3. Main factors involved in pharmaceutical interventions belonging to the five most frequent classifications of Anatomical Therapeutic Chemical (ATC) Level 1, from January to June 2021.

ATC1 and its respective drugs (ATC code)	Frequency (Total = 1,140)
Digestive tract and metabolism (A), n (%)	**243/1,140 (21.3)**
Omeprazole (A02BC01), n (%)	72/243 (29.6)
Lactulose (A06AD11), n (%)	41/243 (16.9)
Bromopride (A03FA04), n (%)	41/243 (16.9)
Metoclopramide (A03FA01), n (%)	26/243 (10.6)
Others, n (%)	63/243 (25.9)
Nervous system (N), n (%)	**221/1,140 (19.4)**
Midazolam (N05CD09), n (%)	52/221 (23.9)
Propofol (N01AX10), n (%)	26/221 (11.9)
Fentanyl (N01AH01), n (%)	24/221 (11.5)
Others, n (%)	119/221 (53.8)
Blood and hematopoietic organs (B), n (%)	**199/1,140 (17.5)**
Enoxaparin (B01AB05), n (%)	94/199 (47.2)
Heparin (B01AB01), n (%)	37/199 (18.6)
Others, n (%)	68/199 (34.2)
General anti-infectives for systemic use (J), n (%)	**151/1,140 (13.2)**
Meropenem (J01DH02), n (%)	73/151 (48.3)
Polymixyn B (J01XB02), n (%)	14/151 (9.3)
Piperacillin + Tazobactam (J01CR05), n (%)	14/151 (9.3)
Others, n (%)	50/151 (33.1)
Sense organs (S), n (%)	**134/1,140 (11.8)**
Methylcellulose (S01KA02), n (%)	133/134 (99.3)
Other ATC codes, n (%)	**192/1,140 (16.8)**

Ninety-one (8.0%) of the interventions documented were directly related to the situations of extreme shortage of medications experienced in the hospital during this period. Sedative midazolam and anticoagulant enoxaparin were the medications with the most critical stock in the period, with limited availability of presentations or even total unavailability at some moments. Consequently, the necessary measures involved readaptation of the standard dilution in the institution and optimization of the available forms, respectively, to meet the clinical demand (Table 4).

All pharmaceutical interventions performed during the study period were listed according to the items of the FASTHUG-MAIDENS mnemonic rule on which follow-up was based, and represented in Table 5. Among these medications, in addition to contributing as the most cited drug in the interventions related to thromboprophylaxis, enoxaparin also corresponded to the highest frequency of interventions related to the medication doses. Among the items from the mnemonic rule, drug indication was associated with nearly 50% (588/1,175) of the interventions

performed, encompassing all the recommendations related to inclusion or discontinuation of medications, readjustment of administration frequency or route, and observations about inappropriate medications due to the patients' clinical situation at the time of the evaluation made by the pharmacist.

Table 4. Frequency of pharmaceutical interventions directly related to shortage in the COVID-19 context and main related drugs from January to June 2021.

Interventions related to shortage	Frequency (Total = 91)
Presentation of the medication not available in the institution, n	53
Midazolam, n (%)	24 (45.3)
Enoxaparin, n (%)	9 (17.0)
Other medications, n (%)	20 (37.7)
Item with critical stock, n (%)	**20**
Enoxaparin, n (%)	14 (70)
Other medications, n (%)	6 (30)
Medication not available in the institution, n	**18**
Enoxaparin, n (%)	7 (38.9)
Other medications, n (%)	11 (61.1)

Discussion

Pharmaceutical performance in the scenario under study was based on institutional and area-specific recommendations about pharmaceutical care for critically-ill COVID-19 patients, aiming above all to provide technical support to the multiprofessional team for safe medication use[16]. In this context, throughout the study period, 88.3% of the patients had at least one potential pharmacotherapy-related problem identified during daily follow-up and, of these, 96.4% had at least one intervention accepted.

The profile of the pharmaceutical interventions tends to coincide with that of the unit and with the care reality of the period under study. In Brazil, a recent study conducted in a university hospital with a similar profile monitored 155 patients between August and November 2019[17]. Conducted in clinical and post-surgical intensive care units, the study evaluated 1,145 interventions, mostly related to antimicrobial therapy (364/1,145) and to aspects such as dilution/reconstitution (86/364) and adequacy of the intravenous infusion rate (21/364). In France, a study carried out in COVID-19 units from a university hospital monitored 238 patients between March and April 2020[18]. A total of 188 interventions were evaluated, mostly related to medications with antithrombotic action (43/188), adjustment in their doses (23/43) and indication for their prescription or discontinuation (16/43). Conducted under similar methodologies, each study evidences different surveillance points relevant to the profile of each unit and to the context experienced, keeping as a common objective the identification and prevention of potential pharmacotherapy-related problems during pharmaceutical performance in the clinical practice.

Absent in the original composition of FASTHUG-MAIDENS, corneal ulcer prophylaxis is part of the pharmacotherapy follow-up routine at HUCFF for patients admitted to intensive care units and who are under continuous sedation. Although there is no consensus in the literature on the best preventive practice or pharmacological prophylactic protocols, some studies suggest that up to 42% of ICU patients may present signs of damage to the corneal surface, with the possibility of progressing to secondary ocular complications[19-20]. Some risk factors for the development of these lesions are as follows: use of ventilatory support, sedation for more than 48 hours, and use of sedatives and neuromuscular blockers[21-23]. The high frequency of interventions observed in terms of this pharmacotherapy aspect, as well as their high acceptance rate, positions it as an important surveillance point in the everyday practice. On the other hand, stress ulcer prophylaxis, originally present in the mnemonic rule, is an essential item in the prescriptions of patients under intensive care. Recommended in different consensuses related to the care of critically-ill patients[24-25], it is mainly indicated for those on mechanical ventilation for more than 48 hours and/or in the presence of coagulopathies, factors common to patients hospitalized in COVID-19 ICUs.

During the study period, there was an increase in consumption of intravenous omeprazole, the only medication standardized for stress ulcer prophylaxis by the institution since suspension of the marketing, distribution and use of Ranitidine by ANVISA in 2020[26]. In parallel, the medication purchase price also rose due to the expanded demand imposed on manufacturers and providers[27].

Table 5. Distribution of the pharmaceutical interventions performed according to the model used for the pharmacotherapy follow-up based on the FASTHUG-MAIDENS mnemonic rule, from January to June 2021.

Domain of the mnemonic rule and its definition		Total interventions by domain	Medication most involved by domain
F	Feeding, n (%)	243	Lactulose, 41 (28.5)
A	Analgesia, n (%)	34	Fentanyl, 24 (70.6)
S	Sedation, n (%)	115	Midazolam, 52 (45.2)
T	Thromboprophylaxis, n (%)	137	Enoxaparin, 94 (68.6)
H	Delirium, n (%)	46	Olanzapine, 32 (69.6)
U	Stress ulcer prophylaxis, n (%)	72	Omeprazole, 72 (100)
G	Glycemic control, n (%)	1	NPH insulin, 1 (100)
M	Medication reconciliation, n (%)	9	Phenobarbital, 2 (22.2)
A	Antibiotics, n (%)	151	Meropenem, 73 (49.6)
I	Drug indications, n (%)	588	Methylcellulose, 133 (22.6)
D	Drug doses, n (%)	138	Enoxaparin, 35 (25.4)
E	Electrolytes and laboratory tests, n (%)	94	Potassium phosphate, 30 (31.6)
N	Absence of interactions, duplicities and adverse reactions, n (%)	29	Fentanyl, 7 (24.1)
S	End of treatment date, n (%)	68	Dexamethasone, 37 (54.4)
Mnemonic rule, n		**1,725**[1]	

[1]It is noted that the sum exceeds the total of interventions (1,140) because one intervention can be related to more than one of the FASTHUG-MAIDENS domains (see Methods).

Between the period prior to the study (May 2020) and the final period (May 2021), the mean unit price paid for the drug by the institution almost tripled, rising from R$ 6.00 to R$ 17.50. In this context, considering all 72 interventions performed for Omeprazole, 36 (50%) suggested changing the administration route prescribed. In order to reconcile rational use of the medication with the reduction in terms of consumption and cost, recommendations were made for the transitions of the parenteral and oral administration routes, according to the clinical and oral viability of the patient evaluated during the pharmacotherapy follow-up review.

Along with Omeprazole, prokinetics and laxatives such as Bromopride and Lactulose, respectively, made up the ATC class most frequently involved in interventions in the current study (A-Digestive tract and metabolism). Most of the interventions involving these drugs were related to their inclusion or discontinuation, totaling 61 interventions of the 82 that were documented for these two classes. According to specific recommendations, use of prokinetics (specifically Metoclopramide) is suggested for critically-ill patients, when employing enteral nutrition and with high risk for bronchoaspiration, as they assist in gastric emptying and in improving tolerance of nutrition itself[28-31] Although there are no specific recommendations for lactulose, a number of articles cite constipation in critically-ill patients on mechanical ventilation as a harmful factor in ventilation weaning[32], which may be aggravated by the extensive use of opioids, common in this context.

Among the most discussed courses of action regarding the COVID-19 treatment in critically-ill patients, Venous Thromboembolism (VTE) prophylaxis was suggested in different emerging guidelines and recommendations[33-34]. Due to the hypercoagulability caused by the immune response to the virus, 50% of the critically-ill patients can develop coagulopathies, increasing the risk of thrombotic events[35].

In the institutional protocol for the use of anticoagulation in COVID-19 patients at HUCFF[36], use of Enoxaparin or Unfractionated Heparin (UFH) was indicated for the prophylaxis of all patients with positive PCR-RT and need for hospitalization, except in the case of contraindications. Daily doses of Enoxaparin 40 mg (for patients weighing from 50 kg to 100 kg) or 5,000 IU of UFH every 8 hours were recommended; with dose corrections or use of an intermediate LMWH dose (Enoxaparin 40 mg every 12 hours) considered on a case-by-case basis.

Despite the number of recommendations and guidelines[37] advocating VTE prophylaxis, especially in this profile of patients, these were based on consensus statements and experts' opinions, as randomized clinical trials were still in progress[38]. However, recent studies also indicated divergences regarding the best dose to be used based on the best clinical outcome and lowest risk of bleeding[39-42]. Therefore, in the absence of evidence to guide choice of the dose to be used, aiming at better prevention of thrombotic events and lower risk of bleeding, clinical judgment and individualized evaluation on a case-by-case basis were crucial. This could be observed in the results of a study carried out by our group[43], in the same unit but in a period prior to that of the current research, where certain variability in the prescriptive behavior regarding enoxaparin was observed, with occurrence of "intermediate doses" higher than the prophylactic ones, but lower than those corresponding to full anticoagulation.

In this context, using pharmacological and non-pharmacological prophylaxis methods for thrombosis represented one of the focus of the interventions performed during follow-up. A total of 136 interventions were performed, among which 37 were related to dose adjustment in the pharmacological prophylaxis used. Of these, 35 were directed at the Enoxaparin doses, a medication that is preferably used for VTE prophylaxis in the institution. A reduction in the dose used was suggested in 25 interventions, due to recommendations regarding dose adjustment according to the decrease in creatinine clearance (<20 ml/min) or to the use of intermediate or therapeutic doses, without a clear clinical justification.

In addition to the systemic complications caused by COVID-19, co-infections and secondary infections, of bacterial and fungal etiology, have been reported as factors associated with increased mortality among critically-ill patients[44]. Mechanisms related to the viral infection itself, such as lymphopenia and immunological impairment, associated with the need for invasive ventilatory support and with the use of central catheters for a prolonged period of time, are elements that favor the development of in-hospital infections. Among the most frequent infections in this scenario, ventilator-associated pneumonia (VAP) and catheter-associated infections are the main causes of bacteremia and severe sepsis, requiring the earliest possible diagnosis and treatment[44].

At HUCFF, the antimicrobial use policy is guided and managed by the Hospital Infection Control Coordination (*Coordenação de Controle de Infecção Hospitalar*, CCIH), through an active daily search, and based on regular microbiological surveillance actions in all sectors of the institution[46]. The guidelines related to the best therapeutic option available are provided by the CCIH, after evaluating the diagnosis and the indication of antimicrobial use, considering data such as action spectrum, dose, administration frequency and treatment length in time. In addition to that, management of the rational use of antimicrobials is carried out through joint and multiprofessional actions between the CCIH medical team and the Pharmacy service, for planning the stock of these medications according to the best cost/benefit ratio.

According to the recommendations standardized by the CCIH at the institution, for general anti-infectives for systemic use, 151 interventions were carried out, including 54 related to adjustment of the antimicrobial dose. Meropenem was the antimicrobial with the highest frequency of interventions (73/151), mostly related to dose adjustment (31/54) and to administration frequency (31/55). Considering the types of infections with the highest occurrence in the scenario evaluated, caused by multidrug-resistant microorganisms, continuous or prolonged infusion of beta-lactam antimicrobials such as meropenem is recommended in order to optimize their bactericidal effect. Dose adjustment of the antimicrobial is indicated in cases of renal function impairment, where creatinine clearance is below 25 ml/min or when it is necessary to use renal replacement therapy[47].

Empirical antimicrobial therapy was recommended by current guidelines during the period[48-49], based on the presence or absence of individual risk factors for the development of infections caused by multidrug-resistant bacteria. These factors include their isolation in potential infectious sites and/or recent hospitalization with exposure to parenteral antimicrobials.

The first half of 2021 was the period with the highest volume of severe cases, ICU admissions and deaths in Brazil since the beginning of the pandemic[50]. During this period, the country experienced fluctuations in the availability of key medications for the treatment of critically-ill COVID-19 patients. These stockouts were experienced by different hospital health services, and brought about an additional obstacle to choosing the best therapeutic regimens and patient safety, requiring articulated strategies to minimize the impact generated on the care provided during that period[51].

In this context, in order to minimize the impacts of shortage on the stock and contribute to the promotion of patient safety, the Pharmacy service resorted to strategies as part of the contingency plan of the HUCFF care support services. Among these strategies, the implementation of the satellite pharmacy in the COVID-19 ICU in June 2020 represented an important contribution both to the monitoring of consumption variations and to control of the stock of medications considered critical in the period, as well as to the pharmacotherapy follow-up and direct interaction with the multiprofessional team. This enabled the medical teams to actively and quickly update on the variations in stock and the need for changes in prescription, as well as enabling discussions about the best available options and therapy for the patients.

At the beginning of 2020, in order to favor access and availability to essential medications used in the treatment of COVID-19, ANVISA established measures to expedite granting and alteration of registrations[52-53] and to expand the offer of available therapeutic options, flexibilizing the technical standards but ensuring efficacy, safety and quality of the process.

This scenario may have been reflected in the important representation of sedatives and analgesics in the interventions (see Tables 3, 4 and 5), as well as in the presence of midazolam, the main item in shortage at HUCFF in the period, as most frequently involved in interventions related to supply. There were 91 interventions related to variability in stock due to shortage, of which 53 signaled the unavailability of drug presentations at the institution, among which 24 specifically involved midazolam. Given the need for advanced support in mechanical ventilation for a large number of patients, variability in the commercial presentations of available medications, especially sedatives, exerted a direct impact on the interventions carried out with the professional teams. Alternation of available sedatives happened in a matter of days, with either midazolam or propofol available, each hour in a different concentration form. The coordinated action of clinical pharmacists with the medical and nursing teams helped to implement the necessary conversions, such as doses and dilutions of different drugs and concentrations, in order to reduce medication errors in this scenario.

The current study presents some limitations related to the context experienced in the period during which the study was conducted and to its very design. Pharmacotherapy follow-up was an activity performed only by the 6 clinical pharmacists and the resident working *in loco* and, in addition to the demands related to the clinical pharmacy, other activities were shared with pharmacy technicians, such as control of local stock, supply and distribution at the satellite pharmacy. Bed-to-bed monitoring of the infusion rates corresponding to the patients' continuous infusions was constantly performed to guide both clinical use and supply, and was fundamental in safely managing the countless alternations of sedative presentations available at each moment. Given this exceptionally dynamic scenario and the intense work volume faced by the team during the period under study, it is estimated than many interventions have been performed verbally. In addition to this, due to the retrospective nature of the study, based on the analysis of care records, data under-documentation may have resulted in an underestimated volume of interventions performed in the period.

Conclusion

COVID-19 imposed particular challenges on the different health systems across the world, whether due to variations in the clinical status of the patients affected or in the changes required in terms of the care routines. Patients admitted to intensive care units need continuous monitoring of different clinical parameters and undergo frequent changes in their pharmacotherapies, increasing the complexity of the care provided. Incorporation of a pharmacist to the multiprofessional team increases the scope of their work in different aspects related to medication use, optimizes pharmacotherapy follow-up and assists in the identification and prevention of drug-related problems. The data obtained made it possible to evaluate points that need more attention during the pharmacotherapy follow-up in the scenario observed, and may be used to guide the formulation of actions aimed at patient safety and protocols targeted at medication use.

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Collaborators

AFP designed the project. JGS and AFP collected, analyzed and interpreted the data. JGS and CAT prepared and reviewed the content of the article. AFP and CAT critically reviewed the intellectual content. The authors assume full responsibility for the data published and guarantee accuracy and integrity of the article.

Conflict of interests statement

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

References

1. Organização Pan-americana da Saúde. Histórico da pandemia de COVID-19. Disponível em: https://www.paho.org/pt/covid19/historico-da-pandemia-covid-19. Acesso em: 25 Nov 2021.
2. Attaway AH, Scheraga RG, Bhimraj A, *et al*. Severe COVID-19 pneumonia: pathogenesis and clinical management. MJ. 2021; 372 (436). DOI:10.1136/bmj.n436.
3. Kordzadeh-Kermani E, Khalili H, Karimzadeh I. Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). Future Microbiol. 2020; 15 (13): 1287- 1305. DOI:10.2217/fmb-2020-0110.
4. Hajjar LA, Costa IBSS, Rizk SI, *et al*. Intensive care management of patients with COVID-19: a practical approach. Ann. Intensive Care. 2020;11(36). DOI: 10.1186/s13613-021-00820-w.
5. Serafim RB, Póvoa P, Souza-Dantas V, *et al*. Clinical course and outcomes of critically ill patients with COVID-19 infection: a systematic review. Clinical Microbiology And Infection. 2020; 27 (1):47-54.DOI:10.1016/j.cmi.2020.10.017.

6. Huang C, Soleimani J, Herasevich S, *et al*. Clinical Characteristics, Treatment, and Outcomes of Critically Ill Patients With COVID-19: a scoping review. Mayo Clinic Proceedings.2021;96(1):183-202. DOI: 10.1016/j.mayocp.2020.10.022.

7. Song Z, Hu Y, Zheng S, *et al*. Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience. Research in Social and Administrative Pharmacy. 2021;17(1):2027-2031. DOI:10.1016/j.sapharm.2020.03.027.

8. BRASIL. Conselho Federal de Farmácia (CFF). Resolução n° 675, de 31 de Outubro de 2019. Regulamenta as atribuições do farmacêutico clínico em unidades de terapia intensiva, e dá outras providências; 2019. Diário Oficial da União, 21 Nov 2019. Seção 1. p. 186.

9. Hospital Universitário Clementino Fraga Filho. Covid-19: 1000 casos notificados no HUCFF. Disponível em: http://www.hucff.ufrj.br/noticias/destaque/1567-covid-19-1000-casos-notificados-no-hucff. Acesso em: 13 Abr 2022.

10. BRASIL. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução n° 7, de 24 de Fevereiro de 2010. Dispõe sobre os requisitos mínimos para o funcionamento de Unidades de Terapia Intensiva e dá outras providências; 2010. Diário Oficial da União, 25 Fev 2010. Seção 1. p. 48

11. Mabasa VH, Malyuk DL, Weatherby EM, *et al*. A Standardized, Structured Approach to Identifying Drug-Related Problems in the Intensive Care Unit: FASTHUG-MAIDENS. Can J Hosp Pharm. 2021; 64 (5); 366-369. DOI: 10.4212/cjhp.v64i5.1073.

12. Vincent, JL. Give your patient a fast hug (at least) once a day. Crit Care Med. 2005; 33(6):1225-1229. DOI: 10.1097/01.ccm.0000165962.16682.46.

13. Aizenstein ML, Tomassi MH. Problemas relacionados a medicamentos, reações adversas a medicamentos e erros de medicação: a necessidade de uma padronização nas definições e classificações. Rev Ciênc Farm Básica Apl. 2011; 32 (2); 169-173.

14. Otero LMJ, Castaño RB, Pérez EM, et al. Actualización de la clasificación de errores de medicación del grupo Ruiz-Jarabo. Farm. Hosp. 2000; 32(1):38-52. DOI: 10.1016/S1130-6343(08)72808-3.

15. World Health Organization. ATC/DDD Index 2022. Disponível em: https://www.whocc.no/atc_ddd_index/. Acesso em: 01 Mar 2022.

16. Associação de Medicina Intensiva Brasileira. Departamento de Farmácia. Recomendações para o Cuidado Farmacêutico ao Paciente Crítico com COVID-19. Disponível em: <https://www.amib.org.br/fileadmin/user_upload/amib/2020/maio/11/RECOMENDACOES_PARA_O_CUIDADO_FARMACEUTICO.pdf>. Acesso em: 01 Jan 2022.

17. Lima IM, Vidigal SB, Lima NM, *et al*. Application of fast-hug-maidens mnemonic and evaluation of its impact in pharmaceutical intervention in an adult intensive care unit. Rev Bras Farm Hosp Serv Saude. 2021;12(1):0566. DOI: 10.30968/rbss.2021.121.0566.

18. Perez M, Masse M, Deldicque A, *et al*. Analysis of clinical pharmacist interventions in the COVID-19 units of a French university hospital. Eur J Hosp Pharm. 2022; 29(1):30-35. DOI:10.1136/ejhpharm-2020-002542.

19. Stafford GS, Pei-Fei L. Eye care in the intensive care unit during the COVID-19 pandemic. Br J Hosp Med. 2020; 81(6):1-10. DOI: https://doi.org/10.12968/hmed.2020.0228.

20. Hearne BJ, Hearne EG, Montgomery H, *et al*. Eye care in the intensive care unit. Journal of the Intensive Care Society. 2018; 19 (4):345-350. DOI:10.1177/1751143718764529.

21. Werli-Alvarenga A, Ercole FF, Botoni FA, Oliveira JMM, *et al*. Lesões na córnea: incidência e fatores de risco em unidade de terapia intensiva. Rev. Latino-Am. Enfermagem. 2011;19 (5). DOI: 10. 1590/S0104-11692011000500005.

22. Azfar MF, Khan MF, Alzeer AH. Protocolized eye care prevents corneal complications in ventilated patients in a medical intensive care unit. Saudi J Anaesth. 2013; 7 (1):33-6. DOI: 10.4103/1658-354x.109805.

23. Mendes JJ, Silva MJ, Miguel LS, *et al*. Diretrizes da Sociedade Portuguesa de Cuidados Intensivos para profilaxia da úlcera de estresse na unidade de terapia intensiva. Rev. bras. ter. intensiva. 2019; 31 (1). DOI: 10.5935/0103-507X.20190002.

24. The BMJ. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. Disponível em: https://www.bmj.com/content/368/bmj.l6722.long. Acesso em: 12 Jan 2022.

25. Associação de Medicina Intensiva Brasileira. Departamento de Farmácia. Recomendações para o Cuidado Farmacêutico ao Paciente Crítico com COVID-19. 2° ed. Disponível em: <https://www.amib.org.br/fileadmin/user_upload/amib/2021/outubro/19/RECOMENDACOES_PARA_O_CUIDADO_FARMACEUTICO1910.pdf>. Acesso em: 12 Jan 2022.

26. BRASIL. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução n° 3.259, de 26 de Agosto de 2020. Proibição- Comercialização, Distribuição, Fabricação, Importação, Manipulação, Propaganda da Ranitidina. Diário Oficial da União, 27 Ago 2020. Seção 1. p. 164.

27. Bionexo. Índice de Preços de Medicamentos para Hospitais (IPM-H). Disponível em: https://pages.bionexo.com/relatorio-fipe-ipm-h#rd-section-joq3m2lv. Acesso em: 12 Jan 2022.

28. Sociedade Brasileira de Nutrição Parenteral e Enteral. Diretrizes Brasileira de Terapia Nutricional. BRASPEN J. 2018;33 (Supl 1):11. Disponível em: https://f9fcfefb-80c1-466a-835e-5c8f59fe2014.filesusr.com/ugd/a8daef_695255f33d114cdf-ba48b437486232e7.pdf. Acesso em: 13 Jan 2022.

29. Campos LF, Barreto PA, Ceniccola GD, *et al*. BRASPEN J. 2021;36(1):122-126. DOI: 10.37111/braspenj.COVID2021.

30. Peng R, Li H, Yang L, *et al*. The efficacy and safety of prokinetics in critically ill adults receiving gastric feeding tubes: A systematic review and meta-analysis. PLoS ONE. 2021;16 (1). DOI: 10.1371/journal.pone.0245317.

31. Hay T, Bellomo R, Rechnitzer T, *et al*. Constipation, diarrhea, and prophylactic laxative bowel regimens in the critically ill: A systematic review and meta-analysis. J Crit Care. 2019; 52:242-250. DOI: 10.1016/j.jcrc.2019.01.004.

32. Azevedo RP, Freitas FGR, Ferreira EM, *et al*. Daily laxative therapy reduces organ dysfunction in mechanically ventilated patients: a phase II randomized controlled trial. Critical Care. 2015; 19 (1). DOI: 10.1186/s13054-015-1047-x.

33. Sociedade Espanhola de Trombose e Hemostasia. Recomendações de Tromboprofilaxia e Tratamento Antitrombótico em pacientes com COVID-19. Disponível em: https://www.covid-19.seth.es/wp-content/uploads/2020/04/Recomendaciones-tromboprofilaxis-y-tratamiento-antitrombotico-pacientes-COVID-19_2020-04-29.pdf. Acesso em: 17 Jan 2022.

34. Marietta M, Ageno W, Artoni A, *et al*. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. 2020;18(3):167-169. DOI: 10.2450/2020.0083-20.

35. Bikdeli B, Madhavan MV, Jimenez D, *et al*. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol. 2020; 75(23):2950-2973. DOI: 10.1016/j.jacc.2020.04.031.

36. Hospital Universitário Clementino Fraga Filho. Uso de Anticoagulantes em Pacientes com COVID-19. Disponível em: http://download.hucff.ufrj.br/DIVULGACOES/2020/COVID_SITE/anticoagulantes%20Covid%20HUCFF.docx.pdf . Acesso em: 17 Jan 2022.

37. Flaczyk A, Rosovsky RP, Reed CT *et al*. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Critical Care. 2020; 24(1):559. DOI: 10.1186/s13054-020-03273-y.

38. U.S. National Library of Medicine. Clinical Trials Gov. Disponível em: https://www.clinicaltrials.gov/ct2/results?term=anticoagulation&cond=COVID-19+AND+%22COVID-19%22&recrs=e&age_v=&age=1&age=2&gndr=&type=&rslt=&Search=Apply. Acesso em: 17 Jan 2022.

39. Chandra A, Chakraborty U, Ghosh S, *et al*. Anticoagulation in COVID-19: current concepts and controversies. Postgrad Med J. 2021; 0:1–8. DOI: 10.1136/postgradmedj-2021-139923.

40. Kollias A, Kyriakoulis KG, Trontzas I, *et al*. High versus Standard Intensity of Thromboprophylaxis in Hospitalized Patients with COVID-19: A Systematic Review and Meta-Analysis. J Clin Med. 2021; 10(23):5549. DOI: 10.3390/jcm10235549.

41. Spyropoulos AC, Goldin M, Giannis D, *et al*. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med. 2021;181(12):1612-1620. DOI:10.1001/jamainternmed.2021.6203.

42. Kollias A, Poulakou G, Dimakakos E, *et al*. Thromboprophylaxis in COVID-19: Early initiation might be as important as optimal dosing. Thromb. Res. 2021; 204: 134–135. DOI: 10.1016/j.thromres.2021.06.004.

43. Pereira MN, Pimentel AF, Junior SC, *et al*. Profile of parenteral anticoagulant use in patients with COVID-19 in a university hospital in Rio de Janeiro. Rev Bras Farm Hosp Serv Saude. 2021;12(3):627. DOI: 10.30968/rbfhss.2021.123.0627.

44. Yang S, Hua M, Liu X, et al. Bacterial and fungal co-infections among COVID-19 patients in intensive care unit. Microbes and Infection. 2021;23(4-5):104806. DOI: 10.1016/j.micinf.2021.104806.

45. Bardi T, Pintado V, Gomez-Rojo M, *et al*.Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis. 2021; 40(3):495-502. DOI: 10.1007/s10096-020-04142-w.

46. Hospital Universitário Clementino Fraga Filho. Coordenação de Controle de Infecção Hospitalar - CCIH. Disponível em: http://www.hucff.ufrj.br/controle-de-infeccao-hospitalar. Acesso em: 24 Fev 2022.

47. Hospital Universitário Clementino Fraga Filho. Antibiótico B-lactâmicos em infusão contínua ou prolongada na pneumonia nosocomial e sepse grave. Disponível em: http://www.hucff.ufrj.br/controle-de-infeccao-hospitalar/protocolos. Acesso em: 25 Fev 2022.

48. Associação de Medicina Intensiva Brasileira. Departamento de Farmácia. Terapia Antimicrobiana Empírica na Síndrome Respiratória Aguda Grave: pelo Comitê de Infecção e Sepse da AMIB. Disponível em: https://www.amib.org.br/fileadmin/user_upload/amib/2020/marco/26/19_Terapia_antimicrobiana_empirica_na_sindrome_respiratoria_aguda_grave_pelo_Comite_de_Infeccao_e_Sepse_da_AMIB.pdf. . Acesso em: 25 Fev 2022.

49. Kalil AC, Metersky ML, Klompas M, *et al.* Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infec Dis. 2016; 63(5):61-111. DOI: 10.1093/cid/ciw353.

50. FIOCRUZ. Boletim do Observatório COVID-19 - retrospectiva 2021. Disponível em: https://portal.fiocruz.br/documento/boletim-do-observatorio-covid-19-retrospectiva-2021. Acesso em: 30 Jan 2022.

51. Sociedade Brasileira de Farmácia Hospitalar (SBRAFH). Levantamento nacional sobre o abastecimento de medicamentos e produtos para a saúde durante o enfrentamento da pandemia pela COVID-19. Disponível em: http://www.sbrafh.org.br/inicial/wp-content/uploads/2020/06/OFICIO-037-Ministro-da-Saude-oficial2.pdf. Acesso em: 19 Jan 2022.

52. BRASIL. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução n° 348, de 17 de Março de 2020. Define os critérios e os procedimentos extraordinários e temporários para tratamento de petições de registro de medicamentos, produtos biológicos e produtos para diagnóstico in vitro e mudança pós-registro de medicamentos e produtos biológicos em virtude da emergência de saúde pública internacional decorrente do novo Coronavírus. Diário Oficial da União, 18 Mar de 2020. Seção 1. p. 59.

53. BRASIL. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução n° 415, de 26 de Agosto de 2020. Define novos critérios e procedimentos extraordinários para tratamento de petições de registro e mudanças pós-registro de medicamentos e produtos biológicos em virtude da emergência de saúde pública internacional decorrente do novo Coronavírus. Diário Oficial da União, 27 Ago de 2020. Seção 1. p. 149.