



Drug utilization in patients with SARS-CoV-2 in an intensive care unit

[Utilización de medicamentos en pacientes con SARS-CoV-2 en una unidad de cuidados intensivos]

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Abstract

Context: Prescription indication studies allow identifying the problems that arise during the use of the drug.

Aims: To evaluate the treatments used in patients diagnosed with SARS-CoV-2 infection hospitalized in critical care service, through a prescription indication study.

Methods: A longitudinal observational study of medication use of the indication-prescription type with elements of the therapeutic scheme and practical consequences was carried out. The sample was characterized from the sociodemographic, clinical, and pharmacotherapeutic points of view. The prescription was evaluated through the indicators: indication, therapeutic scheme, treatment individualization, and drug combinations. The detected adverse reactions were classified according to their causality by the Naranjo Algorithm, their severity, their clinical significance, and according to their mechanism by Rawlins and Thompson.

Results: In the sample (n = 77), the male gender predominated (79%) between 27-59 years old (64%), alcohol consumer (62%), hypertensive (33%) with long hospital stay (51%). A total of 417 medications were analyzed, being antibiotics (50.6%) the most prescribed. 73.4% of the therapeutic schemes were correct; however, 26.6% had problems with the therapeutic schemes due to incorrect doses, intervals, duration of treatment, and risky interactions. According to Rawlins and Thompson, two probable adverse reactions were detected, mild, non-serious, and type A and B.

Conclusions: The results obtained will allow the pharmaceutical professional to create risk matrices that guarantee a timely intervention in the health team to contribute to the rational and safe use of medicines in patients infected with SARS-CoV-2.

Keywords: COVID-19; drug utilization study; indication-prescription; intensive care unit; pharmacoepidemiology; pharmacological treatment.

Resumen

Contexto: Los estudios de indicación prescripción permiten identificar los problemas que se presentan durante el uso del medicamento.

Objetivos: Evaluar los tratamientos utilizados en pacientes con diagnóstico de infección por SARS-CoV-2 hospitalizados en el servicio de cuidados críticos, a través de un estudio de indicación de prescripción.

Métodos: Se realizó un estudio observacional longitudinal del uso de medicamentos, del tipo indicación-prescripción con elementos del esquema terapéutico y consecuencias prácticas. La muestra se caracterizó desde el punto de vista sociodemográfico, clínico y farmacoterapéutico. La prescripción se evaluó a través de los indicadores: indicación, esquema terapéutico, individualización del tratamiento y combinaciones de fármacos. Las reacciones adversas detectadas se clasificaron según su causalidad por el Algoritmo de Naranjo, su gravedad, su significado clínico y según su mecanismo por Rawlins y Thompson.

Resultados: En la muestra (n = 77), predominó el género masculino (79%) entre 27-59 años (64%), consumidor de alcohol (62%), hipertenso (33%) con larga estancia hospitalaria (51%). Se analizaron 417 medicamentos, siendo los antibióticos (50,6%) los más prescritos. El 73,4% de los esquemas terapéuticos fueron correctos, sin embargo, el 26,6% tuvo problemas con los esquemas terapéuticos debido al uso de dosis, intervalos y duración del tratamiento incorrectos, así como interacciones de riesgo. Se detectaron dos probables reacciones adversas, leves, no graves y tipo A y B según Rawlins y Thompson.

Conclusiones: Los resultados obtenidos permitirán al profesional farmacéutico crear matrices de riesgo que garanticen una intervención oportuna en el equipo de salud para contribuir al uso racional y seguro de medicamentos en pacientes infectados por SARS-CoV-2.

Palabras Clave: COVID-19; estudio de utilización de fármacos; pharmacoepidemiología; indicación-prescripción; tratamiento farmacológico; unidad de cuidados intensivos.

ARTICLE INFO

Received: July 6, 2022.

Accepted: September 10, 2022.

Available Online: October 2, 2022.

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INTRODUCTION

According to the most recent reports, the SARS-CoV-2 virus infection has infected 307,155,337 cases worldwide and caused 5,488,628 deaths (World Health Organization, 2022). As of January 2022, 4,125,388 cases and 300,334 deaths have been confirmed in Mexico. In Querétaro, 92,622 confirmed cases and 5,227 deaths had been identified, and specifically in the institution where this study was carried out, a total of 321 confirmed cases were reported until the end of March 2021 and 20 deaths (Gobierno de México, 2022).

One of the current concerns of health professionals working in hospitals is the consequences of using drugs indicated for the SARS-CoV-2 virus. The contribution that a clinical pharmacist can provide in an adult intensive care has a positive impact on the treatment of patients with a high percentage of acceptance on the part of the medical team (Amador et al., 2018).

Prescription indication studies constitute a useful tool to know to what extent there is rationality in therapeutics (Laporte, 1993), as well as to identify the problems that arise during medication use.

The need for a safe and effective therapy to treat SARS-CoV-2 infection motivated the present investigation, whose objective was to evaluate the treatments used in patients diagnosed with SARS-CoV-2 infection hospitalized in the critical care service of the hospital H+ Querétaro, through a prescription indication study in order to contribute to the rational use of medicines used in the treatment of COVID-19.

MATERIAL AND METHODS

General characteristics of the investigation

An observational, longitudinal study of the use of medication of the indication-prescription type with elements of the therapeutic scheme and practical consequences was carried out in patients diagnosed with COVID-19 infection hospitalized in the critical care service of the second-level Hospital H+ Querétaro during the period from December 2020 to March 2021.

Characteristics of the universe and the sample

The sample under study was taken from all the records of patients with COVID-19 infection and confirmed laboratory tests (REAL-TIME PCR) regardless of age and sex who were admitted to the H+ Querétaro hospital in the period from December 2020 to March 2021 and all records that did not report drugs to treat SARS-CoV-2 infection were excluded.

The sample was characterized based on biosocial, clinical, and pharmacotherapeutic variables: age, gender, consumption habits, personal history, the characteristic clinical picture of the disease, specific treatment for COVID-19, and hospital stay.

Ethics approval statement

The research was approved by the Scientific Council of the Hospital Center (PA-2103) and by the Ethics Committee of the Institute of Health Sciences of the Universidad Autónoma del Estado de Hidalgo (UAEH) (UAEH-DI-29-ICSA-FAR-CF-2/Comiteei.icsa 2021/30).

Patient consent statement

The present study did not request the informed consent of the patients. There was no direct contact with the patient, only reading of his clinical file without intervention; however, during the documentary research and data processing, the patient's name and address were omitted. A code with the number of their episode was used in accordance with the provisions of the Mexican data protection law regulated by the National Institute of Transparency, Access to Information and Protection of Personal Data (INAI).

Evaluation of the prescription

The prescription for COVID-19 was analyzed based on the following indicators:

Indication: A necessary and recommended medication was considered when it was indicated according to the WHO COVID-19 clinical management guideline and the clinical guideline for the treatment of COVID-19 in Mexico. (World Health Organization, 2021a; Gobierno de México, 2021).

A: Necessary medication and choice of the recommended one.

B: Necessary medication and choice of the one not recommended.

C: Medicines are not necessary and if they are prescribed.

Therefore, it was defined as:

Correct indication: When the indication corresponded to category A.

Incorrect indication: When it corresponded to category B or C.

Therapeutic scheme: It was taken into account that the dose, frequency, duration of treatment, and route of administration used corresponded to what was

established in the COVID-19 Clinical Management Guide.

Therefore, it was defined as:

Correct therapeutic scheme: When the dose, frequency of administration, duration of treatment, and route of administration used in the prescription corresponded to what is established in the COVID-19 Clinical Management Guide.

Incorrect therapeutic regimen: When the previous condition was not met.

Individualization of treatment: Treatment was considered individualized when age, personal pathological history, the severity of the disease, and contraindications of the indicated medications were taken into account in the prescription.

So, it was defined as:

Individualization of the correct treatment: Taking into account the prescription, the age of the patient, the pathological history, and contraindications of the indicated medications as established in the Clinical Management Guide for COVID-19 and the clinical guidelines for the treatment of COVID-19 in Mexico.

Individualization of incorrect treatment: When the previous condition was not met.

Medication combinations: the therapeutic schemes prescribed to the patient were analyzed to identify the combinations that caused a drug interaction.

The combinations were classified as follows:

Potential: When the combined drugs gave rise to an interaction that was not manifested in the patient but is documented in the literature (Amariles et al., 2021; Rang et al., 2020; Ziehl et al., 2019).

Real: When the combined drugs gave rise to an interaction that was manifested in the patient and was or was not documented in the literature.

Drug interactions detected as a result of drug combinations were classified according to their type and clinical significance as follows:

Beneficial drug interactions: Those drug interactions that modified the effect of one of the drugs for the benefit of the patient.

Risk drug interactions: All those interactions in which the effect of the combined medication was modified, and the same led to risk for the life of the patient.

They were classified according to their clinical significance in High, Moderate, and Low. (Amariles et al., 2021).

Once the evaluation of the drug combinations was carried out, the following was defined:

Correct drug combinations: whether the detected drug combinations led to actual or potential beneficial drug interactions.

Wrong drug combinations: If the drug combinations detected gave rise to potential or real risk drug interactions.

Taking into account the four established indicators (indication, therapeutic regimen, treatment individualization, and drug combinations), the prescription was classified as follows:

Correct prescription: When the adequacy of the four indicators

Incorrect prescription: When two or more indicators do not meet the adequacy.

The adverse drug reactions were identified according to the report made by the health professionals who worked in the intensive care area of the hospital during the study period, which were referred to in the patient's clinical history. For their evaluation, the Naranjo Algorithm was used, and they were classified according to the provisions of the Official Mexican STANDARD NOM-220-SSA1-2016, as well as by their mechanism of action according to the proposal of Rawlins and Thompson.

Statistical analysis

The data obtained from the medical records were processed by calculating and comparing percentages as a summary measure and the Chi-square test (χ^2), establishing a significance level of $p \leq 0.05$.

RESULTS

In the sample ($n = 77$), the male gender prevailed (79%) whose ages ranged between 27-59 years (64%) ($\chi^2 = 3.100$; $p = 0.460$; $p > 0.05$), alcohol consumer (62%) ($\chi^2 = 0.072$; $p = 0.950$; $p > 0.05$), hypertensive (33%) with dyspnea (19%), attack to the general state (17%) and fever (14.6%) as main symptoms of COVID-19 and a long hospital stay (51%). A total of 77 pharmacological treatments and 417 medications were analyzed, being the most prescribed antibiotics (50.6%), followed by anticoagulants (24.7%) and glucocorticoids (21.3%).

In the evaluation of the prescription of the 417 medications indicated to treat COVID-19, 385 corresponded to category A (92%), 21 (5%) to category B, and 11 (3%) to category C. The anticoagulant enoxaparin was the most indicated medication in the sample (96%), followed by the glucocorticoid dexamethasone

(81%) and the antifungal fluconazole (50%). Among the antibiotics, azithromycin (22%) was the most prescribed. On the other hand, fludrocortisone and methylprednisolone were the most prescribed medications as necessary and not recommended (100%), and levofloxacin was the medication not necessary and if prescribed in 33% of the patients who received it.

From these results, 92.5% of correct indications were obtained. They corresponded to category "A" of this indicator, and 7.50% of incorrect indications, as shown in Fig. 1A.

When evaluating the therapeutic scheme indicator, it was obtained that 76.8% of the schemes evaluated were correct. The dose, frequency of administration, duration of treatment, and route of administration used in the prescription corresponded to what was established in the Clinical Management Guide of COVID-19 and was 23.2% incorrect, as shown in Fig. 1B. The biggest problem detected from the pharmaceutical point of view in the said evaluation was the incorrect dose for the drug enoxaparin (81.3%) followed by the incorrect duration of treatment with dexamethasone (14.6%) and the incorrect interval (3.1%) of administration with hydrocortisone.

The individualization of the treatment was correct in 100% of the indicated medications since, in all cases, the age of the patient, his pathological history, and the contraindications of the prescribed medications

were taken into account, as established in the COVID-19 clinical management guide and the clinical guide for the treatment of COVID-19 in Mexico.

Concerning the drug combinations indicator, this was incorrect according to the criteria established for this indicator and from the pharmaceutical point of view, since in 42% of the cases, as shown in Fig. 1C. Risky drug interactions were detected (13), potential type with high clinical significance, with the interaction between moxifloxacin and dexamethasone being the most frequent (38.5%) followed by dexamethasone and levofloxacin (30.8%) (Table 1).

The global analysis of the prescriptions made to treat SARS-CoV-2 infection was correct from the pharmaceutical point of view since 73.4% and 26.6% were incorrect due to errors detected in the indication of methylprednisolone (100%) and enoxaparin (81.3%).

Table 2 shows the causes of the medical staff's errors detected in the prescriptions. As can be seen, the problems in the therapeutic scheme were the most frequent (63.6%).

In the sample study, two adverse reactions were reported in 77 patients, which represented 2.6% of the total number of patients evaluated. Table 3 describes the signs and symptoms of reported adverse reactions and their classification.

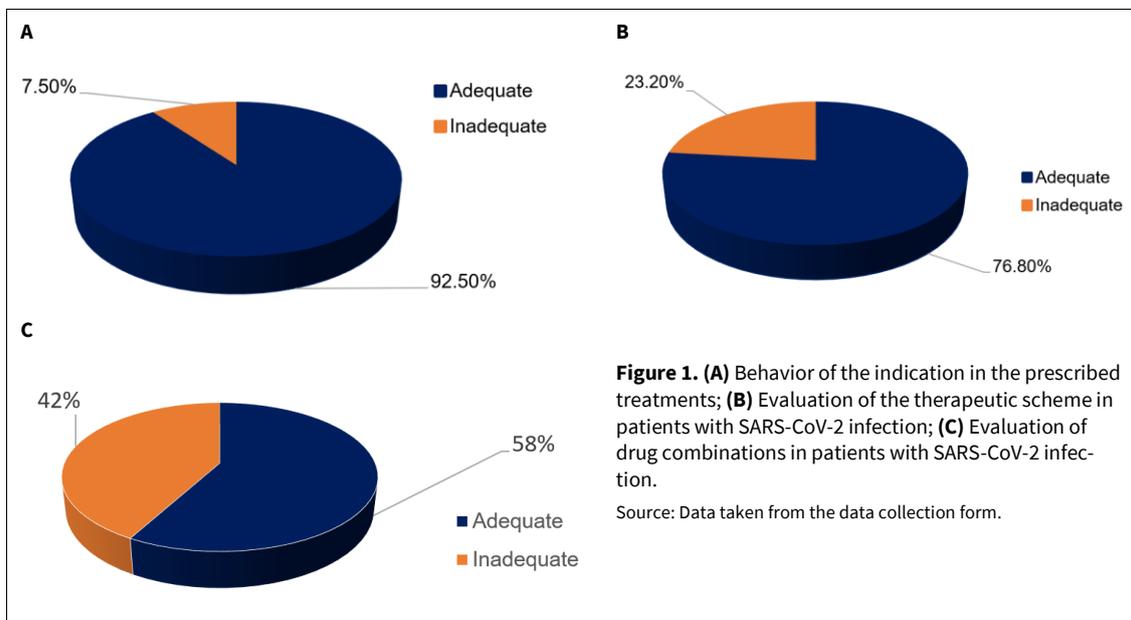


Table 1. Behavior of potential risky drug interactions detected in the treatment of patients with SARS-CoV-2 infection.

Interaction	Type	Total	
		No.	%
Moxifloxacin-Dexamethasone	Risky. High Potential	5	38.5
Dexamethasone-Levofloxacin	Risky. High Potential	4	30.8
Azithromycin-Moxifloxacin	Risky. High Potential	2	15.4
Acetylsalicylic acid-Enoxaparin	Risky. High Potential	1	7.7
Fluconazole-Moxifloxacin	Risky. High Potential	1	7.7
Total		13	100

Source: Data were taken from the data collection form.

Table 2. Errors made in the prescription.

Causes	Total	
	No.	%
Indication problems	42	27.8
Problems with the therapeutic scheme	96	63.6
Problems with drug combinations	13	8.6
Total	151	100

Source: Data were taken from the data collection form.

Table 3 Classification of adverse drug reactions that occurred in the treatment of patients infected with SARS-CoV-2.

Drug	Sign or symptom	Severity	Based on the outcome	Causality (Naranjo algorithm)	Rawlins and Thompson classification
Enoxaparin	Fecal occult blood	Mild	Not Serious	Probable	A
Enoxaparin	Erythema	Mild	Not Serious	Probable	B

Source: Data were taken from the data collection form. A: Independent dose; B: Independent dose.

DISCUSSION

The prevalence of the male gender in patients with COVID-19 has been reported in the consulted literature (Chen et al., 2020; Gadi et al., 2020). It seems to be related to biological factors specific to each gender that underlie the host's immune response and to the lifetime of social, behavioral, and lifestyle factors.

Gadi et al. (2020) report that women tend to produce more effective and better-adapted immune responses to viruses, which translates into less severe cases of COVID-19.

Regarding age, national statistics indicate that people between 30 and 44 years old are the ones who have presented a greater number of positive cases of COVID-19 (Gobierno de México, 2022); however, in Europe, the highest incidence of the disease occurs in patients over 60 years of age (Fantin et al., 2021).

Regarding consumption habits, alcohol consumption was the most frequent. It is known that this substance weakens the immune system by reducing the functions of B lymphocytes, cells responsible for protecting the human body; in addition, excessive consumption increases the risk of acute respiratory distress syndrome, one of the most serious complications of COVID-19 (World Health Organization, 2021b).

Arterial hypertension was the most frequent personal pathological history. In this regard, the literature refers that chronic kidney disease, cardiovascular disease, arterial hypertension, and diabetes are the comorbidities that imply the greatest risk for a serious clinical picture in patients with COVID-19 (Plasencia, 2020), with more than 3.5-fold increases in risk (Fantin et al., 2021).

The signs and symptoms reported by the patients included in the study coincide with those reported by

the Center for Disease Control and Prevention in Wuhan, China (Centers for Disease Control and Prevention, 2021).

The hospital stay of the patients in the sample was long, a similar result to that obtained by Valenzuela et al. (2020), who indicated that the median hospital stay was 13 ± 12 days.

Antibiotics were the drugs most prescribed to patients infected with SARS-CoV-2 that made up the sample, with azithromycin 500 mg being the most used, due to the theory about its anti-inflammatory actions due to dose-dependent suppression of expression perforin and a broad spectrum of proinflammatory cytokines, such as interleukin (IL) 1 beta, IL-6, IL-8, IL-18, and granulocyte-macrophage colony-stimulating factor (Hinks et al., 2021). The recommendations issued by the WHO in the Clinical Management Guide for COVID-19 (World Health Organization, 2021a) do not indicate this drug as the drug of choice for this disease. However, suppose it must be prescribed in patients in serious suspected or confirmed conditions. In that case, it is also recommended to use antibiotic treatment empirical against all the most frequent pathogenic agents, based on clinical criteria, patient characteristics, and the epidemiological situation of the place where it is intended to be used (Gobierno de México, 2021).

Anticoagulants were another pharmacological group frequently indicated in the sample. Studies carried out to conclude that initial treatment with low molecular weight heparin 20 to 80 mg reduces mortality by 48% at 7 days and 37% at 28 days and achieves a significant improvement in the blood pressure-oxygen/inspired fraction ratio of O_2 (PaO_2 / FiO_2) mitigating the formation of microthrombi and the associated pulmonary coagulopathy (Li et al., 2008).

In this study, frequent use of corticosteroids was observed, such as dexamethasone 8 mg, a drug capable of inhibiting tissue damage by reducing the inflammatory response mediated by a decrease in the cytokine storm (Tortosa et al., 2020). A study carried out in 2020 by the United Kingdom demonstrated lower mortality in severe and critical patients who received this drug compared to those who only received standard supportive treatment (Husby et al., 2021; RECOVERY. University of Oxford, 2020).

Fluconazole 100 mg was the most commonly used antifungal agent, which is likely due to the incidence of fungal coinfections. In this sense, Messina et al. (2021) mention the frequency and impact of coinfections that affect patients infected with SARS-CoV-2 due to fungi such as *Candida* spp., invasive aspergillosis, endemic systemic mycoses, and pneumocystosis.

The analysis of the indicators showed that fludrocortisone 0.1 mg and methylprednisolone 500 mg were the most prescribed drugs as necessary and not recommended, which is related to the recommendations expressed in the Clinical Guide for the treatment of COVID-19 in Mexico (Gobierno de México, 2021; World Health Organization, 2021a). Such as levofloxacin, which was not a necessary medication and was prescribed when indicated in a patient with mild symptoms of the disease, in which case the COVID-19 Clinical Management Guide issued by the WHO establishes that there are no criteria to proceed (World Health Organization, 2021a).

During the evaluation of the therapeutic regimen, we found that enoxaparin 20 to 80 mg was the drug with the highest number of incorrect regimens associated with an incorrect dose. This finding coincides with that described by Lamont et al. (2010), who refer to 3.6% of reports related to medication errors due to unfractionated or low molecular weight heparin, in which incorrect doses of enoxaparin are involved.

Risky drug interactions of high clinical significance prevailed in the study, a fact that does not coincide with the results found by Meza et al. (2020), who report that 84.97% of drug interactions in patients hospitalized in an intensive care unit are moderate, followed by those of high clinical significance (9.25%).

The high-risk interaction of moxifloxacin-dexamethasone was the most frequent, followed by dexamethasone-levofloxacin, both have the possibility of increasing the risk of tendinitis and tendon rupture, and although the mechanism of production is unknown, various theories have been proposed, including mechanical stress, direct toxicity on the tendon fibers, inflammatory mechanism with characteristics similar to microcrystalline arthritis, local ischemia and pre-existing alterations in the tendon (Medrano et al., 2007). Therefore, caution is advised if fluoroquinolones are prescribed in combination with corticosteroids, particularly in patients with other concomitant risk factors (age older than 60 years, kidney, heart, and/or lung transplant recipient) (Drugs.com, 2021).

The correct prescriptions were those that prevailed in the study due to the adherence of the medical staff to the national and international guidelines for the treatment of COVID-19 (Gobierno de México, 2021). However, problems were detected in the therapeutic regimens due to the use of incorrect doses, intervals, and duration of treatment, for which the intervention of the pharmacist professional as part of the service's health team is necessary to guarantee the rational and safe use of drugs in these types of patients.

The most frequent cause of errors made in prescriptions by medical personnel were problems in the therapeutic scheme, results that coincide with what Garzón et al. (2020) most important in medication errors.

The two adverse reactions detected in the sample were probable, mild, and not serious and are described in more detail in Table 3. The literature reports that adverse reactions are frequent events in critically ill patients with polypharmacy (Gace, 2012).

In the present study, the incidence of adverse reactions was very low, which is a limitation of this research.

The adverse reactions were taken from the report made in the medical records by the medical and nursing staff. There was no pharmacotherapeutic follow-up by the pharmacist during the pandemic since this professional's access to the intensive care service was restricted to avoid contagion, which made it impossible for the pharmacist to detect adverse reactions through the intensive surveillance method of hospitalized patients.

The adverse reactions detected were related to the drug enoxaparin; in the first case associated with fecal occult blood, this was probably due to heparin-induced thrombocytopenia, since these have a high affinity for platelet factor 4 (PF4), a positively charged tetrameric protein found in the alpha granules of platelets and on the surface of some cells such as endothelial cells and platelets. When heparin and PF4 bind, they form a heparin-PF4 complex that undergoes a conformational change and exposes new epitopes, which act as immunogens (Cruz et al., 2007; Gace, 2012). In a second case related to erythema, probably due to a delayed hypersensitivity reaction itself that involves two stages: the first stage of sensitization in which the immune system reacts for the first time against an antigen (the antigen is presented to T lymphocytes virgins, which produces the activation, expansion, and differentiation of Ag-specific lymphocytes into effector and memory cells), and later stages of triggering after re-exposure to the antigen (where the delayed hypersensitivity reaction occurs when the same antigen is presented to an expanded population of memory T lymphocytes and develops in three successive phases: recognition, activation, and effector phase) (Abbas et al., 2004; Cruz et al., 2007).

CONCLUSION

The prescription of medications in patients infected with SARS-CoV-2 in the critical care unit under study was adequate; however, therapeutic schemes

with errors in the doses, intervals, and duration of treatment, as well as risky drug interactions, were identified. Establishing an intervention program in this hospital in conjunction with its Pharmacotherapeutic Committee is necessary to prevent possible risks associated with these errors in a timely manner.

Likewise, the need to improve care in treatment safety is identified, strengthening pharmacovigilance activity, projecting proactive pharmacovigilance, and using prospective methods that allow a more complete and in-depth analysis of events in patients and, based on this, decision making of effective and efficient pharmacotherapeutic measures.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Special thanks to Hospital H+Queretaro for supplying the data. This research did not receive any specific grant from public, commercial, or not-for-profit funding agencies.

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AUTHOR CONTRIBUTION:

Contribution	Sevilla MM	Téllez AL	Gómez GB	Reyes IH	Velázquez CG	Bermudez IC
Concepts or ideas	x	x		x	x	x
Design						x
Definition of intellectual content		x	x	x		x
Literature search	x		x	x		x
Experimental studies	x					x
Data acquisition	x					x
Data analysis	x	x	x	x	x	x
Statistical analysis	x					x
Manuscript preparation	x					
Manuscript editing	x	x	x	x		x
Manuscript review	x	x	x	x	x	x

Citation Format: Sevilla MM, Téllez AL, Gómez GB, Reyes IH, Velázquez CG, Bermudez IC (2022) Drug utilization in patients with SARS-CoV-2 in an intensive care unit. J Pharm Pharmacogn Res 10(6): 977-985. <https://doi.org/10.56499/jppres22.1460> 10.6.977

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