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Antimicrobial dose adjustment by renal function in adult Intensive Care Unit

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Abstract

Objective: to identify antimicrobial dose adjustments according to renal function in prescriptions for patients hospitalized in an adult ICU of a general hospital in southern Brazil. **Methods:** observational, retrospective cross-sectional study, carried out in an adult ICU of a general hospital in southern Brazil from January to December 2021. All adult patients with ≥48 hours of ICU stay, creatinine clearance (CrCl) ≤60 mL/min/1.73 m^2 and use of one or more of the following antimicrobials: amikacin, ampicillin, ampicillin/sulbactam, cefepime, ceftazidime/avibactam, fluconazole, levofloxacin, meropenem, piperacillin/tazobactam and/or voriconazole. Renal function was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and dose appropriateness was determined by comparing practice to specific guidelines. Sociodemographic variables (gender, age, ethnicity) were evaluated, in addition to the influence of possible determinants, such as: duration of antimicrobial use, length of stay, mortality, among others. **Results:** 151 patients were included, totaling 906 possibilities for adjusting the dose of antimicrobials based on renal function. Among the 906 possibilities, 546 (60.3%) were properly adjusted, 69 (7.6%) were inadequately adjusted, and 291 (32.1%) were not adjusted. Voriconazole was associated with a greater proportion of unadjusted doses 6/6 (100%), while piperacillin/tazobactam was associated with a greater proportion of adjustments not recommended in the literature 41/268 (15.3%). Fluconazole had its doses properly adjusted according to renal function in all situations 21/21 (100%). The duration of antimicrobial use between patients with dose adjustment and those treated with the usual dose was 10 and 11 days, respectively (p <0.001), and the length of ICU stay in the respective groups was 14 and 18 days (p<0.001). **Conclusions:** Our findings revealed a high percentage of antimicrobial dose adjustment according to renal function for ICU patients compared to other studies that evaluated non-critical patients. The data suggest that the involvement of physicians and pharmacists to ensure adequate dosage of nephrotoxic antimicrobials according to renal function has significantly contributed to more favorable patient outcomes.

Keywords: Drug prescriptions; Renal insufficiency; Medication error.

Ajuste de dose de antimicrobianos por função renal em Unidade de Terapia Intensiva adulto

Resumo

Objetivo: identificar a realização de ajuste de dose de antimicrobianos de acordo com a função renal em prescrições de pacientes internados em uma UTI adulto de um hospital geral do sul do Brasil. **Métodos:** estudo observacional, transversal retrospectivo, realizado em uma UTI adulto de um hospital geral do sul do Brasil no período de janeiro a dezembro de 2021. Foram incluídos todos os pacientes adultos com ≥48 horas de internação na UTI, *clearance* de creatinina (ClCr) ≤60 mL/min/1,73m^2 e uso de um ou mais dos seguintes antimicrobianos: amicacina, ampicilina, ampicilina/sulbactam, cefepima, ceftazidima/avibactam, fluconazol, levofloxacino, meropenem, piperacilina/tazobactam e/ou voriconazol. A função renal foi estimada a partir da creatinina sérica usando a equação de Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) e a adequação da dose foi determinada pela comparação da prática com diretrizes específicas. Foram avaliadas variáveis sociodemográficas (sexo, idade, etnia), além da influência de possíveis determinantes, como: tempo de uso do antimicrobiano, tempo de internação, mortalidade, dentre outras. **Resultados:** foram incluídos 151 pacientes, totalizando 906 possibilidades de ajuste de dose de antimicrobianos por função renal. Entre as 906 possibilidades, 546 (60,3%) foram ajustadas adequadamente, 69 (7,6%) foram ajustadas inadequadamente e 291 (32,1%) não foram ajustadas. O voriconazol foi associado à maior proporção de doses não ajustadas 6/6 (100%), enquanto que a piperacilina/tazobactam foi associada a maior proporção de ajustes não preconizados na literatura 41/268 (15,3%). O fluconazol teve suas doses ajustadas adequadamente conforme a função renal em todas situações 21/21 (100%). O tempo de uso de antimicrobiano entre pacientes com ajuste de dose e aqueles tratados com a dose usual foi de 10 e 11 dias, respectivamente (p <0,001), e o tempo de internação na UTI nos respectivos grupos foi de 14 e 18 dias (p <0,001). **Conclusões:** Nossos achados revelaram um percentual elevado de ajuste de dose de antimicrobianos conforme função renal para pacientes em UTI em comparação com outros estudos que avaliaram pacientes não críticos. Os dados sugerem que o envolvimento de médicos e farmacêuticos para garantir a dosagem adequada de antimicrobianos nefrotóxicos de acordo com função renal tem contribuído significativamente para desfechos mais favoráveis para o paciente.

Palavras-chave: Prescrições de medicamentos; Insuficiência Renal; Erro de medicação.

Introduction

Hospitalized patients frequently use a large number of antimicrobials due to their complex clinical conditions. This situation is mainly seen in Intensive Care Units (ICUs) because they are places for easy selection and dissemination of resistant microbial strains[1].

A substantial number of antimicrobials used in the clinical practice have the peculiarity of being eliminated through the kidneys; therefore, renal function impairment can lead to reduced clearance of the drugs and to their consequent accumulation and/or their metabolites in the body, resulting in clinical conditions of intoxication and Adverse Drug Events (ADEs)[2]. Therefore, adequate adjustment of the dose administered in these cases is necessary to guarantee a safe and effective antibiotic therapy and, in addition, it contributes to reducing treatment costs, hospitalization times and mortality[3].

Serum creatinine is the diagnostic marker mostly used to analyze renal function in the clinical practice, indicating the need for dose adjustment, considering the Glomerular Filtration Rate (GFR) through mathematical equations. The equations are grounded on age, gender, body surface, ethnicity and serum creatinine dosage. The most frequently used formulas are the following: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD)[4]. However, a number of studies point out that dose adjustment of the medications prescribed according to renal function is still quite neglected in hospital settings[5,6].

In view of this, the performance of clinical pharmacists by providing pharmaceutical services becomes important. Pharmaceutical care aims at preventing harms to the patients through different actions, including detailed review of prescriptions, therapeutic monitoring, pharmacotherapy follow-up, and health condition management[7,8]. The pharmaceutical intervention for dose adjustment according to renal function aims at evaluating and monitoring the medication doses that, in the context of renal function impairment, can be potentially harmful to the patients[8,9].

However, many doubts persist about the risk and benefits of dose adjustment for different groups of patients, especially those admitted to ICUs. The choice between adjusting the dose and causing therapeutic failure or even death in patients, or not adjusting the dose and subjecting patients to the risk of severe adverse reactions to antimicrobials, represent frequent dilemmas experienced in ICUs. In this sense, the objective of the current study is to identify whether dose adjustment of antimicrobials is performed according to renal function in prescriptions of patients hospitalized in an ICU for adults of general hospital from southern Brazil.

Methods

This is an observational, cross-sectional and retrospective study conducted from January to December 2021 in an ICU for adults of a general hospital from southern Brazil. The aforementioned unit has 20 beds, with a mean of 40 admissions per month, serving both the Unified Health System (*Sistema Único de Saúde*, SUS) and health plans, across several specialties and with outstanding performance during the COVID-19 pandemic[10].

The prescriptions included in the study were those from patients older than 18 years of age, of both genders, hospitalized in the ICU from January to December 2021, with hospitalization times over 48 hours, CrCl ≤60 mL/min/1.73 m^2, and using one or more of the following antimicrobials: amikacin, ampicillin, ampicillin/sulbactam, cefepime, ceftazidime/avibactam, fluconazole, levofloxacin, meropenem, piperacillin/tazobactam, and/or voriconazole. The antimicrobials considered for the study were chosen among the nephrotoxic antimicrobials most frequently prescribed in the ICU during 2021, determined in a previous analysis. Vancomycin was not included in the study for having a specific dose adjustment protocol already instituted, related to monitoring its serum level. Patients who did not have a daily serum creatinine laboratory evaluation during the study period and/or who started using the antimicrobials selected outside the study period were excluded.

The study sample was assembled after a retrospective evaluation of all the prescriptions of patients hospitalized in the ICU who met the inclusion criteria. The data were collected by means of the Tasy® hospital management system and the NoHarm.ai® Artificial Intelligence tool, which is used for the pharmaceutical evaluation of prescriptions in the institution and compiled in a *Microsoft Office Excel®* structured spreadsheet.

For each patient, Creatinine Clearance (CrCl) was calculated in the CKD-EPI calculator, recommended by most of the medical team members to assess patients' renal function. To evaluate the frequency of antimicrobial dose adjustment by renal function, CrCl was assessed by reference values and staging according to the Kidney Disease Outcomes Quality Initiative (KDIGO) for adults: from 59 to 45 mL/min/1.73 m^2 (G3a stage), from 44 to 30 mL/min/1.73 m^2 (G3b stage), from 29 to 15 mL/min/1.73m^2 (G4 stage), <15 mL/min/1.73 m^2 (G5 stage)[11]. To evaluate dose and frequency adjustment corresponding to administration of the antimicrobials prescribed according to renal function, the following databases were used: Micromedex®[12] and UpToDate®[13]m as well as The Sanford Guide to Antimicrobial Therapy (2021)[14].

For each possibility of dose adjustment according to renal function, the following outcomes were verified: adjustment made spontaneously by the prescriber - adequate/inadequate adjustment; adjustment made after the pharmaceutical intervention - adequate/inadequate adjustment; or if no dose adjustment was made. It is worth noting that, for the antimicrobials, they were only considered as not adjusted and/or as inadequate adjustments (dosage regimen different from the consulted literature) after the loading dose (>24h).

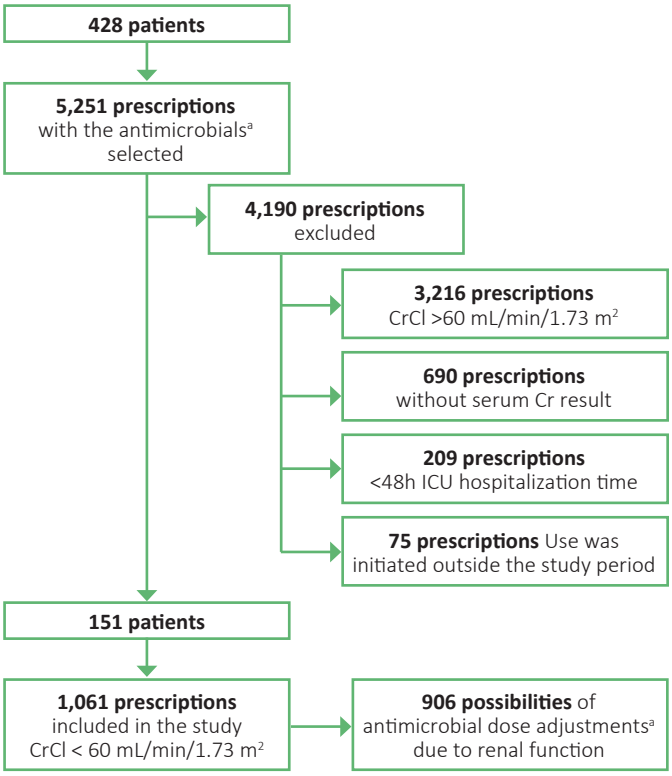
Sociodemographic variables were also collected (gender, ethnicity and age), as well as reason for ICU admission by main anatomical system according to the International Classification of Diseases and Health-Related Problems (ICD), Renal Replacement Therapy (RRT), antimicrobial use time, ICU hospitalization time, C-reactive protein (CRP) and leukocytes tests on the days corresponding to the antimicrobial dose adjustment opportunity. In addition, the hospital discharge or death outcomes were also collected.

SPSS v.28 was used for the statistical analysis. The data were presented as absolute and relative frequencies, when dealing with categorical variables. The numerical variables were described using mean values and standard deviations or through medians and interquartile ranges. The association between the variables was assessed by means of Pearson's chi-square test, along with the analysis of the adjusted residuals. All tests were two-tailed, with their significance level defined at $p<0.05$. The study was approved by the institution's Research Ethics Committee (*Comitê de Ética em Pesquisa*, CEP), under opinion No. 3,919,556.

Results

During the period analyzed, 151 ICU patients met the study inclusion criteria and 906 prescriptions with opportunities for antimicrobial dose adjustment by renal function were identified (Figure 1).

Figure 1. Inclusion diagram corresponding to the sample



[a]The following antimicrobials were considered: amikacin, ampicillin, ampicillin/sulbactam, cefepime, ceftazidime/avibactam, fluconazole, levofloxacin, meropenem, piperacillin/tazobactam and voriconazole. CrCl: Creatinine Clearance; Cr: Creatinine; ICU: Intensive Care Unit

Predominance of the male gender was noticed among those who required dose adjustment (N=79; 52.3%). The mean age ± standard deviation (SD) was 63.7 ± 14.2 years old; and infectious diseases stood out as the main cause of ICU admission. The median days of use for the antimicrobials selected was 9 days; in turn, the ICY hospitalization time presented a median of 14 days. These and other descriptive variables of the sample can be seen in Table 1.

Table 1. Sociodemographic and clinical characteristics of the patients using antimicrobials selected from January to December 2021 in the ICU for adults of a general hospital from southern Brazil.

Variables	n=151
Age (years old) – Mean ± SD	63,7 ± 14,2
Gender– n (%)	
Male	79 (52,3)
Female	72 (47,7)
Ethnicity – n (%)	
White	139 (92)
Brown	7 (4,7)
Black	5 (3,3)
Reason for ICU admission – n (%)	
Infectious diseases	58 (38,4)
Circulatory system diseases	19 (12,6)
Digestive system diseases	17 (11,3)
Sepsis	16 (10,6)
Respiratory system diseases	11 (7,3)
Neoplasms (tumors)	10 (6,6)
Genitourinary system diseases	8 (5,3)
Others	12 (7,9)
RRT – n (%)	
Yes	30 (19,9)
No	121 (80,1)
Number of ATBs – Median (P25 – P75)	2 (1 – 3)
ATB use time (days) – Median (P25 – P75)	9 (7 – 11)
CRP (mg/L) - Median (P25 – P75)	148,1 (89,4 – 228,6)
Leukocytes (µL) - Median (P25 – P75)	14.980 (8.660 – 21.230)
ICU hospitalization time (days) – Median (P25 – P75)	14 (9 – 21)
Outcome – n (%)	
Discharge	58 (38,4)
Death	93 (61.6)

TRS: terapia renal substitutiva; ATB: antimicrobianos; PCR: proteína C reativa; UTI: unidade de terapia intensiva.

A total of 906 prescriptions with dose adjustment possibilities of antimicrobials due to renal function were identified. Table 2 presents the frequency of dose adjustment due to renal function for each antimicrobial.

Table 2. Frequency of antimicrobial dose adjustment according to renal function in patients hospitalized in the ICU for adults of a general hospital, from January to December 2021.

	Spontaneous adjustment by the prescriber			Adjustment by pharmaceutical intervention			
Antimicrobial	**n (%)**	**Adequate n (%)**	**Inadequate n (%)**	**Adequate n (%)**	**Inadequate n (%)**	**Adjustment not performed n (%)**	**p-value***
Meropenem	376 (41.5)	243 (64.6)*	17 (4.5)	8 (2.2)	0 (0)	108 (28.7)	
Piperacillin/tazobactam	268 (29.6)	95 (35.4)	41 (15.3)*	4 (1.5)	0 (0)	128 (47.8)*	
Amikacin	74 (8.2)	52 (70.3)*	6 (8.1)	0 (0)	0 (0)	16 (21.6)	
Ceftazidime/avibactam	60 (6.6)	42 (70)*	2 (3.3)	7 (11.7)*	0 (0)	9 (15)	
Ampicillin/sulbactam	46 (5.1)	28 (60.9)	0 (0)	2 (4.3)	0 (0)	16 (34.8)	**<0.001**
Ampicillin	24 (2.6)	23 (95.8)*	0 (0)	0 (0)	0 (0)	1 (4.2)	
Cefepime	23 (2.5)	15 (65.2)	3 (13)	1 (4.4)	0 (0)	4 (17.4)	
Fluconazole	21 (2.3)	21 (100)*	0 (0)	0 (0)	0 (0)	0 (0)	
Levofloxacin	8 (0.9)	5 (62.5)	0 (0)	0 (0)	0 (0)	3 (37.5)	
Voriconazole	6 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)*	
Total	906 (100)	524 (57.8)	69 (7.6)	22 (2.5)	0 (0)	291 (32.1)	

*Statistically significant association by testing the residuals adjusted at 5% significance (p<0.05).

Among the possibilities identified, appropriate dose adjustment of antimicrobials by renal function was present in 546 (60.3%) prescriptions, with clinical pharmacists being responsible for recommending dose adjustments in 22 (2.5%) prescriptions, and the remaining dose adjustments (524; 57.8%) made spontaneously by physicians. Fluconazole had its doses adjusted according to renal function in all possibilities: 21/21 (100%). Pharmaceutical interventions for dose adjustment were implemented in 26 (2.9%) situations from all possibilities identified, if which 22 (84.6%) were accepted. Ceftazidime/Avibactam was the medication with the highest number of pharmaceutical interventions (11.7%).

It was observed that, in 69 (7.6%) situations, the dose adjustment of antimicrobials by renal function performed by the physicians was not in line with the literature consulted by the researchers, resulting in 36 (52.2%) underdose cases and 33 (47.8%) overdose cases, when compared to the doses recommended in the literature. Piperacillin/Tazobactam was associated with the highest proportion of inadequately adjusted doses: 41/69 (59.4%).

Among all 291 (32.1%) possibilities of unadjusted doses, voriconazole was associated with the highest proportion (6/6 [100%]), followed by piperacillin/tazobactam in 128/268 (47.8%) of the cases. The number of patients who received at least one inadequate and/or unadjusted dose of antimicrobials according to renal function was 85, representing 56.3% of all 151 study patients.

Table 3 presents the chi-square association test results, taking as the dependent variable the adjustment of antimicrobial doses properly performed *versus* the sum of inadequate adjustment and non-adjustment. Patients with diagnoses of neoplasms and genitourinary tract diseases presented more adequate dose adjustments according to renal function, when compared to other diagnoses (p<0.001). Patients that were not subjected to hemodialysis had more unadjusted antimicrobial doses and/or inadequate adjustments, when compared to those undergoing hemodialysis (p<0.001). In most of the situations, it was observed that the estimated CrCl was in the G3b and G4 stages. However, most of the dose adjustment possibilities of antimicrobials due to renal function were properly performed in the G3a stage (p=0.041). The group of patients with dose adjustments that followed recommendations based on CrCl values presented shorter antimicrobial use times (p<0.001). the ICU hospitalization times were shorter among the patients that had their doses adjusted than in those whose dosage was not adjusted and/or inadequately adjusted (p<0.001).

Table 3. Associations of dose adjustment by renal function according to sociodemographic and clinical characteristics of the patients hospitalized in the ICU for adults of a general hospital, from January to December 2021.

Variables	Adequate adjustment (n=546)	Inadequate adjustment▲ (n=360)	p-value*
Age (years old) – Mean ± SD	64.3 ± 12.3	63.6 ± 13.8	0.427
Gender – n (%)			0.498
Male	285 (52.2)	197 (54.7)	
Female	261 (47.8)	163 (45.3)	
Reason for ICU admission – n (%)			**<0.001**
Infectious diseases	199 (36.4)	145 (40.3)	
Circulatory system diseases	67 (12.3)	51 (14.2)	
Digestive system diseases	96 (17.6)	50 (13.9)	
Sepsis	42 (7.7)	48 (13.3)*	
Respiratory system diseases	42 (7.7)	34 (9.4)	
Neoplasms (tumors)	43 (7.9)*	13 (3.6)	
Genitourinary system diseases	24 (4.4)*	3 (0.8)	
Others	33 (6.0)	16 (4.4)	
RRT – n (%)			**<0.001**
Yes	121 (22.2)*	12 (3.3)	
No	425 (77.8)	348 (96.7)*	
CrCl (mL/min/1.73 m²) – n (%)			**0.041**
G3a	56 (10.3)*	23 (6.4)	
G3b	192 (35.2)	144 (40.0)	
G4	195 (35.7)	141 (39.2)	
G5	103 (18.9)	52 (14.4)	
CRP – Median (P25–P75)	139.2 (73.4 –228.4)	123.1 (60.9 –203.8)	0.103
Leukocytes – Median (P25–P75)	12.830 (7.730 –18.740)	13.015 (8.650 –21.647)	0.075
ATB use time (days) – Median (P25–P75)	10 (7 – 15)	11 (8 – 15)	**<0.001**
ICU hospitalization time (days) – Median (P25–P75)	14 (9 – 19)	18 (14 – 26)	**<0.001**
Outcome – n (%)			0.478
Discharge	185 (33.9)	113 (31.4)	
Death	361 (66.1)	247 (68.6)	

RRT: Renal Replacement Therapy; CrCl: Creatinine Clearance; CRP: C-Reactive Protein; ATB: Antimicrobial; ICU: Intensive Care Unit.
▲Inadequately adjusted antimicrobials correspond the sum of the inadequately adjusted and unadjusted ones.
*Statistically significant association by testing the residuals adjusted at 5% significance (p<0.05).

Discussion

A large number of published studies have focused on evaluating medication dosages in patients with renal failure in non-critical conditions[15,16,17,18,19,20,21]. However, many doubts persist about the risk and benefits of dose adjustment for different groups of patients, such as those admitted to ICUs. To the authors' knowledge, this study is the first to evaluate the performance of antimicrobial dose adjustments in prescriptions for patients in an ICU for adults of a general hospital from the Brazilian South region.

The current study identified that, among 906 antimicrobial prescriptions that required dose adjustment, 60.3% were adjusted properly and that the remaining 39.7% of the prescriptions with inappropriate dosages were divided into 32.1% of not adjusted prescriptions and 7.6% adjusted inappropriately by the medical team. These findings corroborate those obtained by Camargo *et al*. (2019), who reported that, of the 168 dose adjustment possibilities, 99 (58.9%) adjustments were performed in the ICU of a tertiary-level hospital from the Brazilian Northeast region[22].

In our study, the percentage of adequate adjustments was considerable higher than in other countries: India (19%), Palestine (26.4%), Lebanon (37%) and South Africa (41%)[18,19,20,21]. However, our results are similar to those found in research studies conducted in developed countries, where the adherence rate varies from 50% to 87%[23,24]. Nevertheless, our study was conducted in an ICU and the previous ones were carried out in hospitalization units or wards, which somehow hinders the comparison. Possibly, the criticality level of the ICU patients in this study has contributed to a more careful evaluation of their prescriptions, which might justify this high percentage of dose adjustments according to renal function when compared to literature data referring to prescriptions for patients in inpatient units or wards.

Meropenem was the antimicrobial most frequently prescribed in our study, and its dose adjustments were performed properly in 66.8% of the cases. Additionally, fluconazole was the eighth most prescribed antimicrobial, but had its doses adjusted according to renal function in all 21/21 situations (100%), demonstrating knowledge on the part of the prescribers. Similar data were found in a study by Rodrigues *et al.* (2021) conducted at a university hospital from northeastern Brazil, which also evaluated the frequency of dose adjustments according to the patients' renal function[17].

Ceftazidime/Avibactam was the antimicrobial with the most pharmaceutical interventions; this finding can be explained by the fact that it is the only one of the antimicrobials selected in the study to be part of the antimicrobial stewardship program implemented by the Clinical Pharmacy service and the Hospital Infection Control Service (*Serviço de Controle de Infecção Hospitalar*, SCIH) of the institution. Stewardship aims at optimizing antibiotic therapy in the treatment of infections, considering proper indication, dose and duration for better outcomes and to prevent adverse events[25].

Despite the low number of pharmaceutical interventions found in the study (2.8%), which can be related to the development process of the Clinical Pharmacy service in the study hospital, which has more than 1,200 beds, only 4 clinical pharmacists and 4 Pharmacy residents to evaluate the patients' daily prescriptions, a high rate of acceptance by the medical team was detected (22/26 [84.6%]); this finding reinforces the need for clinical pharmacists' performance in the team.

In a retrospective study, Cabello *et al.* evaluated the impact of pharmaceutical interventions on a monitoring program for patients with renal failure in a hospital from Spain. In this study, clinical pharmacists accounted for 74% of drug dose adjustments by renal function and showed that pharmaceutical interventions contributed significantly to improving the patients' renal function[26].

The rate of inadequate prescriptions obtained in our study was 39.7%, resulting in possible antimicrobial underdose or overdose case. It is worth noting that doses below the therapeutic range may cause reduced therapeutic efficacy, whereas doses prescribed above the recommended in patients with decreased CrCl may cause increased serum concentrations, resulting in increased toxicity risks[27,28].

Several reasons can contribute to inadequate adjustments and/or non-adjustment of antimicrobial doses in the face of renal failure. There are inherent difficulties in reviewing renal function tests before prescribing an antimicrobial, which is reflected in the number of exclusions due to absence of the serum creatinine test in our study, for example. In addition to that, the study was conducted in an ICU with high rates of infections caused by multidrug-resistant microorganisms, where the vast majority of treatments are initiated with maximum doses and maintained to avoid septic shock[29].

Aligned to this, our study identified that, in fact, patients with sepsis had fewer adjusted doses of antimicrobials according to renal function when compared to other clinical diagnoses, such as neoplasms and genitourinary tract diseases. This finding can be explained due to variations in the distribution and clearance volumes in septic patients, which can affect concentration of the antimicrobials; for this reason, many prescribers choose not to adjust the dose and assume the risk of overdosing, aiming at microbiological cure[30].

When using renal elimination medications, pharmacokinetic and pharmacodynamic parameters should be considered In this context, antimicrobials are classified into concentration- or time-dependent. Medications are considered concentration-dependent when the effect on bacterial death is higher as the antimicrobial serum concentration increases, regardless of the exposure time, as is the case of aminoglycosides. Examples of time-dependent antimicrobials, with the most important factor for clinical response being the exposure time to the drug, include betalactams[30,31]. However, when considering the frequency of dose adjustments made compared to the number of dose adjustment possibilities by renal function identified for each antimicrobial, there was no predominance between adjustments for concentration- or time-dependent antimicrobials, thus evidencing lack of knowledge among physicians and pharmacists about all the antimicrobials that required dose adjustments.

Piperacillin/Tazobactam was a medication that generated many doubts during prescription, resulting in 41/268 (15.3%) cases of incorrect adjustments and in 128/268 (47.8%) cases of non-adjustment. Piperacillin/Tazobactam is widely used in ICUs for the treatment of in-hospital and healthcare-associated infections such as pneumonia, complicated urinary tract infection and febrile neutropenia, among others[32]. Choice of the dosage regime for this antimicrobial is based on the type of pathogen involved. However, it was verified that its use was inadequate in more than half of the therapeutic episodes, where a full dose was administered every 12 hours. This dosage regime was not found in the guidelines and books referenced, emphasizing the team's lack of knowledge[11,12,13].

Similarly, in a cohort study, Dewitt *et al*. (2016) identified higher prevalence of incorrect dose prescriptions for piperacillin/tazobactan in an ICU[33].

In addition to that, it was verified that voriconazole did not have its doses adjusted according to renal function in any of the opportunities identified: 6/6 (100%). In patients with moderate to severe renal failure (CrCl <50 mL/min/1.73 m^2), there may be accumulation of the sulfobutyl ether β-cyclodextrin sodium (SBECD) excipient present in the injectable formulation, thus increasing the nephrotoxicity risk. In these situations, the literature recommends prioritizing the oral formulation[34]. However, for being a study conducted in an ICU, most of the patients did not have the oral route available, making use of enteral tubes for drug administration. In this context, the pharmaceutical form is oftentimes altered to enable administration of solid medications via this route. This practice is more prone to generating ADEs such as errors in dilution and administration of inadequate dose, among others, thus hindering achievement of the desired serum level when compared to the injectable formulation of voriconazole, and this is a plausible risk-benefit reason for low adherence to dose adjustments according to renal function, as there is no culture of serum level dosing of this medication in the institution, which generates unawareness about whether there is underdose or toxicity related to this medication[35].

In addition, underestimation of the impact of more advanced stage kidney disease by physicians resulted in higher inadequate adjustment rates in the G3b, G4 and G5 stages of kidney disease *versus* less advanced stages of renal impairment. Similarly, in a prospective study conducted at an ICU, Sedaghat *et al.* (2021) identified that dose adjustments are frequently neglected in the severe stages of renal failure[36]. However, in a study conducted in Ethiopia, it was found that higher serum creatinine made physicians pay more attention to drug prescription and lower dosage errors were obtained, which differs from previous research studies and from our finding[3]. Due to criticality of the patients in this study with high chances of progressing to septic shock, it is believed that the physicians chose to use antimicrobial doses above the amount required based on renal function due to uncertainty about the optimal level since, in the study field, serum monitoring of any of the selected antimicrobials is not performed, possibly leading to uncertainties.

Another finding of our study was that the patients on hemodialysis presented lower inadequate adjustment rates when compared to those undergoing hemodialysis. This result can be related to the performance of nephrologists along with the ICU team, resulting in more careful prescriptions for these patients. Findings that are consistent with our result are described by Saad *et al*. in a study conducted in 2019 at two university hospitals from Lebanon[16].

As for the mortality rates and the CRP and leukocytes results, there was no significant difference between patients receiving doses adjusted according to renal function and those that did not have their doses adjusted, thus indicating that the practice of dose adjustment according to renal function exerted no influence on the patients' favorable clinical outcomes.

However, our results diverge from those found in a retrospective cohort study which revealed that antibiotic dose adjustment according to CrCl in ICU patients with renal failure significantly increased the treatment failure and death risks[22]. Even so, both results need to be interpreted with caution, as inadequate antimicrobial choice can influence therapeutic failures and cause increased mortality. In addition, for being a study conducted in an ICU, higher mortality rates are already expected due to the patients' severity levels.

When antimicrobial use time and ICU hospitalization time were evaluated, it was found that, in both outcomes, there was a significant reduction in days for patients who had their antimicrobial doses adjusted according to renal function when compared to those who did not have their doses adjusted and/or had inadequate adjustments. Findings consistent with this result have been described in previous studies which reported that the involvement of physicians and pharmacists to ensure appropriate antimicrobial dosage according to renal function was associated with shorter intensive care unit hospitalization times, fewer adverse events and reduced treatment costs[37,38,39,40].

The data from our study should reduce the uncertainty surrounding the decision to adjust antimicrobial doses in ICU patients with impaired renal function, as the results found from this practice showed benefits both to the patients (reduction in the antimicrobial use time and in the ICU hospitalization time) and to the hospital, contributing to reducing treatment costs. Furthermore, the findings reinforce the importance of the pharmacists' role in making these adjustments in an appropriate way, reasserting the role of these professionals with the multidisciplinary team in patient care and clarifying doubts about medications. It is understood that this study promoted strengthening and expansion of the antimicrobial prescription analysis service for renal failure in the institution where the research was conducted.

However, the results found need to be interpreted with caution because this was a single-center study, which limits generalization of the results. The CKD-EPI formula was chosen to estimate the GFR in the current study, although it may not be suitable for patients with high muscle mass and those with malignant conditions such as neoplasms. In addition to that, the physicians may have consulted different dose adjustment guidelines than those selected by the researchers and/or it is plausible that the dose of some antimicrobials may have been adjusted based on different clinical outcomes. Finally, for being a retrospective study, the relationship between inadequate use of nephrotoxic antimicrobials and occurrence of ADEs was not analyzed.

Conclusion

Our findings reveal a high percentage of antimicrobial dose adjustment according to renal function for patients admitted to the ICU, when compared to other studies that evaluated non-critical patients. In addition to that, the results suggest that the involvement of physicians and pharmacists to ensure appropriate dosage of nephrotoxic antimicrobials according to renal function has significantly contributed to more favorable outcomes, such as decreased antimicrobial use times and ICU hospitalization times.

It is expected that this study will contribute to strengthening actions such as including clinical pharmacists in the team, in order to conduct the pharmacotherapy follow-up of patients with decreased renal clearance.

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Collaborators

CR participated in project design, data collection, treatment and analysis, and review and approval of the final version, in addition to responsibility for the article for publication. KF participated in project design, in addition to collaborating in data collection, treatment and analysis, and review and approval of the final version for publication. ALC participated in project design, in addition to collaborating in data analysis, and review and approval of the final version for publication.

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Declaration of conflicts of interest

The authors declare no conflicts of interest.

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