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ORIGINAL ARTICLE

Evaluation of Antimicrobial Dose Adjustment Based on Renal Function in Intensive Care Units

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Highlights:

1. Among the most nephrotoxic drugs prescribed in ICU, we underline the following antibiotics: piperacillin + sulbactam, ampicillin + sulbactam, meropenem, teicoplanin and vancomycin.
2. Patients who received an interconsultation from the nephrologist and an assessment from the clinical pharmacist were more likely to have their dose adjusted than those who did not receive an interconsultation, showing the importance of specialized follow-up.
3. Association between changes in the glomerular filtration rate of critically ill patients and antimicrobial dose adjustment, showing a significant association with the clinical outcome of the assessed patients.

ABSTRACT

Objetive: To identify the factors associated with the adjustment of the dose of antimicrobials based on renal function in patients admitted to Intensive Care Units (ICUs). Method: Cross-sectional, descriptive--analytical study with data collection referring to the period from July to December 2019 in three ICUs. Patients hospitalized in these units with prescription of antimicrobials were included, and subjects with a stay of less than 24 hours in the ICU and aged less than 18 years were excluded. The association between dependent and independent variables was tested through univariate analysis, using a binary logistic regression model. The magnitude of the association was calculated using odds ratios (OR) with 95% confidence intervals (CI) and $p < 0.05$. Results: Of the total of 290 patients, 55.0% were male and 54.1% older adults (≥ 60 years). A total of 738 antimicrobials were used; 276 of them required dose adjustment, and 99.6% were adjusted. Piperacillin + Tazobactam, and Ampicillin + Sulbactam wre the most frequently adjusted. Altered creatinine (OR=9.753 CI=6.876–13.833), consultation with the Nephrologist (OR=4.431 CI=3.035–6.470) and pharmaceutical follow-up (OR=1.415 CI=1.046-1.914) were statistically associated with performing dose adjustment based on glomerular filtration rate (GFR). Conclusion: The findings revealed a significant association between changes in GFR and creatinine and the adjustment of the antimicrobial dose. There was a high level of dose adjustment and a statistical association between altered creatinine, consultation with a nephrologist and pharmacotherapeutic follow-up with the adjustment, reinforcing the importance of specialists and clinical pharmacists in the ICU.

Keywords: Anti-infective agents; Acute kidney injury; Calculation of drug dosage.

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INTRODUCTION

With the use of sulphamides, in 1936, the modern era of pharmacological treatment of infections began. With the increase in scientific development, the use of these drugs has been disseminated, and the irrational use is one of the factors that contribute to the increase in microbial resistance, configured as a public health problem of great relevance[1,2]. Microbial resistance is characterized as a health threat, since the emergence of new vulnerability patterns is superior to the emergence of new antimicrobials (ATM)[1,3].

In Intensive Care Units (ICUs), the use of ATM inducing cases of acute kidney injury (AKI), correspond to the most common adverse effect, reaching 36.0%. The effects may originate from the different classes of ATM, however, the prevalence may vary according to some factors such as the population studied, the dose used and the time of treatment[4,5].

The diagnosis of AKI is frequent in ICUs[6,7], and can be explained by the diversity of diseases that can cause some loss or damage in the control of self-regulation of patients' organs[8]. AKI is also understood as a serious health problem since it is related to high rates of morbidity and mortality, increased length of stay and associated costs[5, 9].

Renal injury decreases the plasma clearance of drugs, which have a mechanism of elimination dependent on the functionality of the kidneys. Therefore, drugs, especially ATM, which are considered to be major causes of bacterial resistance and some as nephrotoxic drugs, can accumulate in the body if administered in their usual doses, leading to cases of intoxication[10]. Therefore, it is necessary to adjust the dose according to the patient's renal function, based on the glomerular filtration rate (GFR)[7]. In a study carried out at the Hospital Center of the University of Coimbra[11], 57.9% of adverse reactions to drugs that led to hospitalization, or that occurred during hospitalization, could have been avoided, and most of them occurred due to failure to adjust the dose.

Thus, the objective of this study was to identify the factors associated with the dose adjustment of antimicrobials based on renal function in patients admitted to ICUs.

METHODS

Type of study and research location

This is a cross-sectional, descriptive-analytical study. The information used for this study was extracted from the research database "Pharmaceutical Care: evaluation of drug use in a regional hospital".

The study was carried out in a public hospital located in a municipality in the Southwest region of Bahia, which has an open door hospital profile of medium and high complexity, with the main focus on the care of Urgencies and Emergencies, and also a reference in orthopedic surgeries. At the time of collection, it had 275 beds, 29 of which were in the ICU (expanded to 373 beds, 39 of which were in the adult ICU)[12].

This hospital serves the population of 26 municipalities, being a reference in the southwestern region of Bahia. It performs urgent and emergency care, with risk classification according to state protocol[12], medical clinic, clinical neurology, neurosurgery, general surgery and orthopedics, pediatrics (urgent and emergency, ward and ICU) and psychiatry.

Sample and inclusion and exclusion criteria

The study sample consisted of patients admitted to the ICU who used any class of systemic--acting ATM (belonging to group J of the Anatomical Therapeutic Chemical (ATC) classification of

the World Health Organization (WHO)), during hospitalization regardless of the number of days of treatment and with a length of stay greater than 24 hours in the ICU. Patients under the age of 18 years were not included in the sample, as shown in Figure 1.

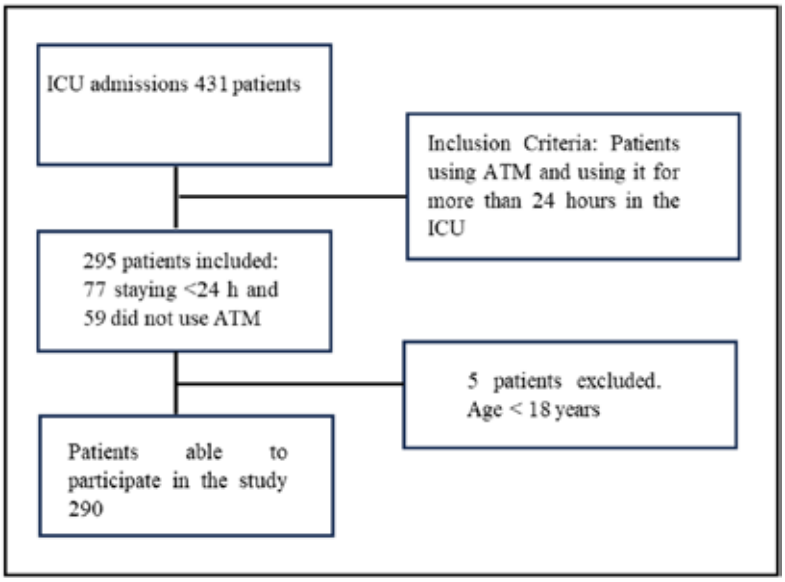

Figure 1 – Diagram of the process of inclusion of patients in the study. Bahia, Brazil.

Data Collection

Data were collected by filling out a specific form, prepared for the research, based on the patients' medical record. A pilot test was carried out with the collection instrument, in which the medical records of ten patients who were not part of the sample for this study were analyzed. The research considered the period from July to December 2019, and data collection was carried out by a previously trained team.

Definitions of variables:

Dependent variable

Renal function was assessed using GFR, calculated using the Cockcroft-Gault (CG) equation [CG: (140-age) x weight/(72 x creatinine) x 0.85 (if female)][13], when weight is available, and/ or by the *CKD-EPI* equation[14] GFR = 141 X min (CRS/k, 1) at X max (CRS/k, 1) -1.209 X 0.993 Age X 1.018 [if female] X 1.159 [black], when patient race is available. Both calculators are available on the website of the Brazilian Society of Nephrology (BSN).

The CG equation was chosen for its national and international acceptance in studies aimed at evaluating renal function and in studies with medications[15,16,17].

The weight used in the aforementioned equation, estimated weight, was obtained from the patient's medical record, collected from the nutritional anamnesis, calculated according to the patient's sex[18].

The dose adjustment evaluation was based on GFR, hierarchical and divided into two categories: altered when GFR < 60 ml/min/1.73m² and unchanged when GFR > 60 ml/min/1.73m² [19]. The need for dose adjustment was assessed individually for each ATM, based on GFR ranges.

The adjustment and dose of the ATM were evaluated according to the package insert of the professional present in the electronic bulletin of the National Health Surveillance Agency (ANVISA)

and with the Micromedex® Drugdex database, accessible by smartphone application (MICROMEDEX, 2018)[20]. For hemodialysis, GFR < 15 ml/min/1.73m² was considered [21] and the adequacy of the adjustment was evaluated according to the indication for this GFR range.

Independent variables

The serum creatinine value was categorized as elevated creatinine when it presented an increase of ≥ 0.3 mg/dL in 48 hours or an increase of 1.5 times in relation to the presumed baseline serum creatinine of the last seven days, at any time of hospitalization[21] and creatinine within the normal range when serum creatinine was between 0.5 and 1.5 mg/dL, based on the parameter of the Laboratory of the Hospital Unit of study.

Sociodemographic variables regarding sex (female and male) and age (categorized in the age groups 18 to 59 years and equal to or above 60 years - non-older adults and older adults) were collected.

As for the clinical variables, health conditions, pharmacotherapy and multiprofessional care were collected: Diabetes Mellitus (DM), Systemic Arterial Hypertension (SAH), heart disease, cancer, liver disease and nephropathy, use of vasoactive drugs, use of sedatives, hemodialysis, interconsultation with nephrologist and pharmaceutical evaluation categorized qualitatively into objective alternatives containing the option “yes” or “no”. On the other hand, the clinical outcome was categorized as death and not death (the latter being discharge, transfer or avoidance).

The use of nephrotoxic drugs (angiotensin-converting enzyme inhibitors - ACEI, H2 receptor antagonists, K^+-sparing agents, carbapenem, thiazide and osmotic diuretics, beta-blockers, polymyxins, penicillins, cephalosporins, aminoglycosides, macrolides, glycopeptides, quinolones, platelet aggregation inhibitor and antiviral) was evaluated according to the classification adapted from the Clinical Practice Guideline for Acute Kidney Injury[21], and categorized into: use during hospitalization yes or no.

Data analysis

Descriptive analysis was performed, estimating the absolute and relative frequencies of categorical variables and measuring the central tendency (mean and median) and dispersion (standard deviation and interquartile range) of continuous variables. To evaluate the normal distribution of continuous variables, the *Kolmogorov-Smirnov* test was used, considering p>0.05 normal distribution. *Pearson*’s chi-square test and *Fisher*’s exact test were used to compare the proportions of categorical variables.

The association between dependent and independent variables was performed through univariate analysis, using the binary logistic regression model. The magnitude of the association was calculated using odds ratio (OR) with 95% confidence intervals (CI) and significance level of 0.05.

Ethical considerations

This research met all ethical precepts. The study “Pharmaceutical Care: evaluation of drug use in a regional hospital” was approved by the Ethics and Research Committee (ERC) of the State University of Southwest Bahia. Candeias/BA, Brazil, UESB, protocol number 4,229,023, CAAE 34826020.1.0000.0055.

RESULTS

Of the 290 patients analyzed, 55.0% were male. The median age of the patients was 62 years with an interquartile range of 27. The median length of stay was 9.0 days, with an interquartile range

of 12. The predominant age group was ≥ 60 years (54.51%). Regarding comorbidities, 60.2% had SAH, 32.6% DM and 20.1% heart disease.

There was a statistical association between altered GFR and age group ≥ 60 years, in which these patients were 5.158 times more likely to have altered GFR compared to non-older patients (OR=5.158, CI= 3.24 – 8.21). Another association found was with heart disease comorbidity, with a 4.952 times chance of presenting altered GFR when compared to those who did not present this comorbidity (OR=4.952, CI=2.06 – 11.92), table 1.

In the study, 738 ATM were used, with a mean of 2.54 ± SD ± 1.36 ATM per patient, of which 276 required dose adjustment, and 99.6% were performed. The most prescribed ATM and also the most involved in dose adjustment were Piperacillin + Tazobactam, and Ampicillin + Sulbactam, followed by Teicoplanin, Vancomycin and Meropenem, Table 2.

Table 1 – Binary logistic regression between sociodemographic and clinical variables and glomerular filtration rate for each antimicrobial used by patients admitted to the Intensive Care Unit of a public teaching hospital. Bahia, Brazil. (N=738)

Sociodemographic and clinical variables	**GFR**		**p-value***	**OR (95% CI)**
	Non altered N (%)	**Altered N (%)**		
Sex				
Male*	166 (41.8)	231 (58.2)		1
Female	87 (27.8)	226 (72.2)	<0.0001	1.867 (1.359 – 2.565)
Age range				
18-59 years*	184 (56.4)	142 (43.6)		1
≥ 60 years	69 (17.7)	321 (82.3)	<0.001	6.028 (4.291 – 8.469)
Systemic arterial hypertension				
Yes*	107 (28.2)	272 (71.8)		1
No	91 (39.7)	138 (60.3)	0.003	1.676 (1.185 – 2.370)
Diabetes mellitus				
Yes*	49 (24.5)	151 (75.5)		1
No	141 (36.5)	245 (63.5)	0.003	1.774 (1.209 – 2.601)
Heart disease				
Yes*	8 (10.0)	72 (90.0)		1
No	127 (39.0)	199 (61.0)	<0.001	5.744 (2.676 – 12.326)
Use of vasoactive drugs				
Yes*	142 (30.2)	328 (69.8)		1
No	11 (45.5)	133 (54.5)	<0.001	1.928 (1.400 – 2.654)
Use of sedation				
Yes*	153 (31.4)	334 (68.6)		
No	100 (43.7)	129 (56.3)	0.001	1.692 (1.224 – 2.339)

Source: Elaborated by the authors. GFR = glomerular filtration rate. * Binary logistic regression, p<0.05 significant. OR: Odds Ratio. CI: 95%Confidence Interval

Table 2 – Association between ATC level 3 classification of antimicrobials and the need for dose adjustment, according to GFR, in patients admitted to the Intensive Care Unit of a public teaching hospital. Bahia, Brazil.

ATC Level 3	Antimicrobials	Need for Dose Adjustment	
		No N (%)	Yes N (%)
J01D	Meropenem Cefepime	158 (69.0)	71 (31.0)
J01C	Piperacillin/Tazobactam Ampicillin/Sulbactam	93 (52.2)	85 (47.8)
J01X	Teicoplanin Vancomycin Polymyxin B	86 (54.4)	72 (45.6)
J01F	Azithromycin Clindamycin	63 (95.5)	3 (4.5)
J01G	Amikacin Gentamicin	16(51.6)	15 (48.4)
J01M	Ciprofloxacin Levofloxacin	9 (42.9)	12 (57.1)
J02A	Fluconazole	5 (29.4)	12 (70.6)
J01E	Sulfamethoxazole + trimethoprim;	3 (75.0)	1 (25.0)
J05A	Acyclovir	3 (37.5)	5 (62.5)
J04A	Ripe (rifampicin, isoniazid, pyrazinamide and ethambutol)	1 (100.0)	0
A07A	Nystatin	1 (100.0)	0

Source: Elaborated by the authors. *Pearson's chi-square, p<0.05 significant. ATC: Anatomical Therapeutic Chemical Code. GFR = glomerular filtration rate.

Altered creatinine, inter-consultation with the Nephrologist, pharmaceutical evaluation and death outcome are statistically associated with dose adjustment for each ATM, table 3. Patients with altered creatinine were 9.753 times more likely to undergo dose adjustment than those with unaltered creatinine (OR= 9.753, CI=6.876 – 13.833). Patients who received inter-consultation with the Nephrologist were 4.431 times more likely to undergo dose adjustment than those who did not receive inter-consultation (OR=4.431, CI=3.035 – 6.470).

Table 3 – Binary logistic regression between clinical variables and dose adjustment for antimicrobials from patients admitted to the Intensive Care Unit of a public teaching hospital. Bahia, Brazil. (N=715)

Variables	ATM dose adjustment		p-value*	OR (CI)
	No N (%)	Yes N (%)		
Altered creatinine				
No	343 (82.3)	74 (17.5)		1
Yes	96 (32.2)	202 (67.8)	<0.001	9.753 (6.876 – 13.833)
Nephrologist Inter-consultation				
No	387 (69.1)	173 (30.9)		1
Yes	52 (33.5)	103 (66.5)	<0.001	4.431 (3.035 – 6.470)
Pharmaceutical evaluation				
No	251 (65.2)	134 (34.8)		1
Yes	188 (57.0)	142 (43.0)	<0.001	1.415 (1.046 – 1.914)
Outcome				
Non-death	301 (78.4)	83 (21.6)		1
Death	138 (41.7)	193(58.3)	<0.001	5.072 (3.658 – 7.032)

ATM: antimicrobial. Non-death: discharge and transfer. *Binary logistic regression, p<0.05 significant. OR: Odds Ratio. 95% Confidence Interval
Source: Elaborated by the authors.

Table 4 shows the class of nephrotoxic drugs, as well as the drug corresponding to each subgroup, used by patients admitted to the ICU. The most prescribed drugs were Ranitidine 66.7%, those belonging to the Penicillins and beta-lactamase inhibitors (Piperacillin + Sulbactam and Ampicillin + Sulbactam) 48.4% and Carbapenem (Meropenem) 26.4%.

Table 4 – Distribution of the frequency of nephrotoxic drugs used in patients admitted to the Intensive Care Unit of a public teaching hospital. Bahia, Brazil. (N=788)

Nephrotoxic drugs	Drug	N (%)
H2-receptor antagonists	Ranitidine	230 (29.2)
Penicillin and Beta-lactamase Inhibitor	Piperacillin + Sulbactam Ampicillin/Sulbactam	167 (21.2)
Carbapenems	Meropenem	91 (11.5)
Glycopeptide	Teicoplanin and Vancomycin	86 (10.9)
Platelet aggregation inhibitor	Acetylsalicylic acid	45 (5.7)
ACEI	Captopril, Enalapril	32 (4.1)
Aminoglycosides	Amikacin and Gentamicin	28 (3.6)
Polymyxins	Polymyxin B	23 (2.9)
Quinolones	Cipro and Levofloxacin	20 (2.5)
Beta blockers	Metoprolol	17 (2.2)
Thiazide diuretic	Hydrochlorothiazide	15 (1.9)
K^+ -sparing agents	Spironolactone	15 (1.9)
Osmotic diuretic	Mannitol	12 (1.5)
Antiviral	Acyclovir	7 (0.9)

ACEI: angiotensin-converting enzyme inhibitors. K^+: potassium. Cipro: ciprofloxacin.

Source: Elaborated by the authors.

DISCUSSION

The present research conducted with critically ill patients identified the need to adjust the dose of antimicrobials in ICU patients based on their renal function. In view of the global public health problem configured by bacterial resistance, the rational use of ATM is a substantial alternative in the search for reducing hospital infection rates and reducing microbial resistance mechanisms, seeking to reduce mortality rates, hospitalization time and costs in patient therapy.

Studies on renal toxicity report that the nephrotoxic potential of drugs used in the ICU is high, contributing to the occurrence of AKI cases [5,9,22]. Their nephrotoxic potential can be intensified when used simultaneously, such as the finding in the study in which more than 70% of patients who developed AKI used such agents simultaneously, especially with antimicrobials[22].

Regarding the study population, the patients admitted to the ICU were mostly male, a finding that can be justified by the fact that they did not seek primary care services when compared to females, thus being more vulnerable to diseases, especially severe and chronic diseases, in addition to having a shorter life expectancy[23].

The aging of the population has culminated in an increase in the mean age of ICU patients, since the older adults usually present more severe diseases and make more significant use of health services. In this study, the group formed by patients aged ≥ 60 years represented the majority of the population, which may be related to the physical changes that can be combined, predisposing high-risk conditions and vulnerability to diseases[24].

This finding corroborates the data in the literature, which show the advancement of age as an independent prognosis for the development of AKI cases[5,6]. The kidney presents structural and functional changes that, when associated with chronic diseases, make this group more likely to AKI, as they present lower kidney functionality and reduced GFR[5,6,24]. Its incidence varies according to the clinical condition of the patient, with greater visibility in ICU[6].

In the present study, comorbidities SAH, DM and heart diseases were predominant, and these clinical characteristics are potential risk factors for renal impairment; nephrons, filtering units of the kidneys are injured by SAH, a condition that limits or prevents the removal of waste and excess fluid from the blood, predisposing to AKI. Meanwhile, DM triggers a progressive increase in urinary albumin excretion accompanied by a decline in glomerular filtration/creatinine clearance[25].

Regarding heart diseases, cardiorenal syndrome (CRS) can be seen in patients who have heart failure, a term that refers to the joint dysfunction of the heart and kidneys, resulting in a kind of cascade of feedback mechanisms causing damage to both organs. The term CRS is often used to relate the pathophysiological interaction between the two organs, and can be divided into “cardiorenal”, when cardiac dysfunction leads to renal dysfunction and “renocardiac”, when primary renal dysfunction leads to cardiac dysfunction[26].

The use of vasoactive and sedative drugs showed a significant relationship with the alteration of the GFR of the patients. A similar result was presented by a study carried out in a medium-sized public Regional Hospital in the municipality of Floriano/Piauí. The literature shows the use of vasoactive drugs as a risk factor for ICU mortality, due to the hemodynamic instability of patients and due to the vasoconstriction resulting from the use of these drugs[8].

It is estimated that the risk of developing AKI increases threefold in patients who use ATM, compared to those who do not [6]. In ICUs, the use of these drugs is usually made for an exacerbated time, especially in infectious processes where there are the development of numerous cases of renal lesions, with aminoglycoside antimicrobials and polymyxins being the main responsible for the loss of renal function. If the degree of renal injury is low, the loss of renal function may be reversible, but in severe cases it can lead to death, and this loss of function is one of the causes aggravating the general condition of the patients[9].

Given the nephrotoxic profile, these drugs can accumulate in the body when administered in their usual doses, making it necessary to adjust the pharmacological dosage based on the patients’ renal function[7,27]. The prescription of ATM should not be based only on empirical therapy, it should be carried out rationally, based on laboratory results, and not only on epidemiological data of certain etiological agents, as usually occurs, which leads to unnecessary and excessive consumption, making the development of resistance favorable[28,29].

Of the antimicrobials prescribed in this study, broad-spectrum penicillins, glycopeptides, and carbapenems were the ATM classes most involved in dose adjustment. In the literature, these three ATM groups are the most prescribed in the ICU[24]. The use of these drugs can be justified by the fact that they are initially used as empirical therapy in cases of severe infections[29].

The group of beta-lactams, including penicillins, cephalosporins, carbapenems and monobactams are recognized as nephrotoxic. Among the possible mechanisms of injury, the most common are represented by transport to the cell tube, acylation of target proteins and lipid peroxidation. In the clinic, several types of kidney injury have been described, including glomerulonephritis, ATN (acute tubular necrosis) and AIN (acute interstitial nephritis)[30].

The use of beta-lactams and the incidence of ARF has not yet been fully elucidated. However, penicillins and cephalosporins are associated with less renal toxicity when compared to carbapenems. In the case of the combination of some penicillins, such as piperacillin-tazobactam, when used together

with vancomycin, there are reports of a significant increase in the incidence of ARF, compared to the use of vancomycin alone[31].

Nephrotoxicity has been a major concern for vancomycin use. The literature reports the increased risk of kidney injury with vancomycin. The onset of AKI occurs about 4 to 8 days of therapy, with subsequent improvement after discontinuation of drug therapy. The underlying supported mechanisms from several studies are pro-inflammatory oxidation, mitochondrial dysfunction, and cellular apoptosis leading to proximal tubular injury and, when extensive, also ATN, AIN has been seen in several patients, usually with cutaneous manifestations. The exact prevalence of ATN or AIN is still unknown, given low availability of renal biopsy, poor serum quality and urine biomarkers, and frequent use of combinations of antimicrobials with high nephrotoxic potential. General risk factors include pre-existing kidney disease, disease severity, and concomitant use of nephrotoxic drugs[32].

In the present study, there was a significant association between GFR, altered creatinine and death outcome with the performance of dose adjustment for ATM in patients admitted to ICUs, as well as the performance of interconsultation with a nephrologist and pharmaceutical evaluation, data that are directly related to the population studied. The early identification of AKI is directly related to the better prognosis of critical clinical patients, with the measurement of biological markers being the most used tools for this diagnosis, based on the analysis of laboratory data, which indicate acute changes that interfere with renal function[6,27]. Loss of GFR is a late marker of kidney injury, so the application of measures against nephrotoxicity, such as dose adjustment, minimization of non-essential medications or particularly toxic combinations and correction of hypovolemia, should be implemented. In this study, altered GFR and creatinine were associated with dose adjustment[6,27].

Critical patients and patients with AKI are subject to higher morbidity and mortality, so we can infer that in this study, although the dose adjustment is related to the outcome of death, this measure should be implemented as soon as possible so as not to worsen the patients' clinical condition or even increase morbidity and mortality. Study shows that pharmacological monitoring of Vancomycin did not affect AKI reduction (OR 1.061, 95% CI 0.948-1.187), but reduced 30-day mortality (OR 0.873, 95% CI 0.821-0.929)[32].

Hospital areas classified as high risk, such as ICUs, should be monitored by a clinical pharmacist[33]. Resolution number 675/2019[33] of the Federal Council of Pharmacy (FCP) regulates the attributions of the clinical pharmacist in the ICU and defines as one of his attributions, the analysis of the patient's prescription regarding legal and technical aspects, in order to promote the appropriate use of medications, nutrients and other health products[33]. Goto et al. (2022)[32] cite that pharmacological management of vancomycin for individual patients, by pharmacists and multiprofessional team, was effective in reducing AKI and mortality in 30 days.

The literature reports that the intervention of the nephrologist, when carried out in an adequate time, has a positive impact on the evolution of the patients with AKI, mainly in the determination of measures such as: dose adjustment or suspension of potentially nephrotoxic drugs, adequate volume resuscitation and earlier institution of dialysis[34]. The literature also shows as a problem reported by nephrologists the fact that they are only called in ICUs in very advanced stages of AKI, making it more difficult to find treatment alternatives that would be more effective if, for example, they were applied in the early stages of the lesion[34].

The most important problems related to patients with kidney injury are medication dosing errors, where an inadequate dose can cause toxicity or an ineffective therapy. Given the specific risks of using nephrotoxic drugs, these should be prescribed with caution and dosage recommendations should be strictly followed. Drug accumulation and toxicity can develop rapidly if dosages are not adjusted. Correctly adjusting the dose of drugs in renal dysfunction contributes to fewer adverse

events, reduces therapeutic costs, length of hospital stay and mortality, in addition to maintaining therapeutic efficacy[7].

The most frequent nephrotoxic drugs in this study were H2 Receptor Antagonists (ranitidine), Penicillin and Beta-lactamase Inhibitor (Piperacillin + Tazobactam /Ampicillin + Sulbactam) and Carbapenem (Meropenem). The literature reports that among the main risk drug classes for the development of AKI are aminoglycosides, glycopeptides and polymyxins[22]. In the case of antimicrobials, nephrotoxicity depends on the concentration used and the time of treatment or prophylaxis.

It is possible to observe as signs of AKI with the use of aminoglycosides and polymyxins, for example, the increase in serum creatinine and urea concentration, hematuria, proteinuria, oliguria, glycosuria, uricosuria, hypocalcemia and hyperkalemia, among other electrolyte changes. In the case of polymyxins, their toxicity is due to the presence of fatty acids and the d-aminobutyric acid component in the drug, which trigger the process of edema and cell lysis by increasing membrane permeability[35]. Regarding the nephrotoxic profile of polymyxin B, at the time the study was carried out, the Hospital followed the package insert of the drug in its dose adjustment protocol, and this brought the information that it was necessary to adjust the dose according to the GFR. However, recent studies show that there is no need to adjust in the scenario of acute kidney injury[36, 37].

As limitations of the present study, we can mention the impossibility of deepening discussions due to the fact that the patients were not monitored.

On the other hand, the results found demonstrate the high frequency of alteration of GFR in critically ill patients, as well as the use of inadequate doses of antimicrobials, which can culminate in high morbidity and mortality rates, highlighting the need for strategies aimed at the rational use of antimicrobials, including dose adjustment, in addition to the search for developing strategies jointly with a multidisciplinary team, in order to ensure patients' safety.

CONCLUSION

In this study, the findings revealed a significant association between changes in GFR and creatinine and antimicrobial dose adjustment. There was a high dose adjustment and statistical association between altered creatinine, consultation with a nephrologist and pharmacotherapeutic monitoring with the adjustment, reinforcing the importance of specialists, clinical pharmacists in the ICU, as well as the development of protocols and permanent education of health professionals.

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