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Polymyxin-B and vancomycin-associated acute kidney injury in critically ill patients

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ABSTRACT

Background: This study aims to investigate renal toxicities of Polymyxin B and Vancomycin among critically ill patients and risk factors for acute kidney injury (AKI).

Methods: This is a cross-sectional study conducted with patients admitted to an intensive care unit (ICU) of a tertiary hospital in Brazil. Patients were divided into two groups: those who used association of Polymyxin B + Vancomycin (Group I) and those who used only Polymyxin B (Group II). Risk factors for AKI were also analyzed.

Results: A total of 115 patients were included. Mean age was 59.2 ± 16.1 years, and 52.2% were males. Group I presented higher GFR (117.1 ± 70.5 vs. 91.5 ± 50 ml/min/1.73 m^2, $p = 0.02$) as well as lower creatinine (0.9 ± 0.82 vs. 1.0 ± 0.59 mg/dL, $p = 0.014$) and urea (51.8 ± 23.7 vs. 94.5 ± 4.9 mg/dL, $p = 0.006$) than group II on admission. Group I also manifested significantly higher incidence of AKI than group II (62.7% vs. 28.5%, $p = 0.005$), even when stratified according to RIFLE criteria ('Risk' 33.9% vs. 10.7%; 'Injury' 10.2% vs. 8.9%; 'Failure' 18.6% vs. 8.9%; $p = 0.03$). Accumulated Polymyxin B dose > 10 million IU was an independent predictor for AKI (OR = 2.72, 95% CI = 1.13–6.51, $p = 0.024$).

Conclusions: Although patients who received Polymyxin B plus vancomycin had more favorable clinical profile and higher previous GFR, they presented a higher AKI incidence than those patients who received Polymyxin B alone. Cumulative Polymyxin B dose > 10 million IU was independently associated to AKI.

KEYWORDS
Polymyxin B; acute kidney injury; vancomycin; drug toxicity

Introduction

Acute kidney injury (AKI) is a frequent complication in critically ill patients admitted to intensive care units (ICU). It has been recognized as a major risk factor for chronic kidney disease (CKD) [1,2]. Drug-related nephrotoxicity is among the most common etiologic factors for AKI [3].

Polymyxin B is an exclusive intravenous gram-negative specific antimicrobial. It has been widely used in recent years for multidrug resistant infections [4]. Renal toxicity remains Polymyxin's most important side effect, which affects 6 to 54% of patients [5]. In most cases, Polymyxin B-related AKI presents with a non-oliguric and non-dialytic course, and it usually happens after a week of drug administration [5].

Vancomycin is a glycopeptide antimicrobial used for gram-positive infections, mainly for methicillin-resistant *Staphylococcus aureus* (MRSA). Nephrotoxicity is a well described side effect of this drug, though its mechanism has not been completely elucidated yet [6].

Combination of polymyxin B with other antibiotics has been used for treatment of resistant bacterial infections [7]. Antibiotics resistance is currently a worrying public health problem since it is increase in all parts of the world, which led the World Health Organization to recently publish a strategic global plan to control this problem [8]. The association of polymyxin B with vancomycin is used mainly in the context of infection by *Acinetobacter baumanni*, and efficacy of this combination has yet been demonstrated [7,9], and it is one of the last therapeutic options against multi-drug resistant bacteria. The main adverse effect of this antimicrobial combination is renal toxicity, once Vancomycin significantly increases the risk of AKI [5,7].

Antimicrobial-related nephrotoxicity in critically ill patients is not uncommon, and AKI in this group of patients leads to higher morbidity and mortality. Therefore, the aim of this study was to investigate renal toxicities of Polymyxin B and Vancomycin among critically ill patients and risk factors for AKI.

Methods

Study design and patient's selection

This is a cross-sectional study conducted with patients admitted to the ICU of a tertiary hospital in Fortaleza,

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Northeast Brazil, in a 3-years period (from January 2012 to December 2014), who used Polymyxin B or Vancomycin.

Selection criteria were:

- Patients ≥ 18 years;
- Use of Polymyxin B associated or not with Vancomycin;
- Use of Polymyxin B or Vancomycin for at least three consecutive days;
- Admission in the ICU in the study period.

Exclusion criteria were:

- Patients admitted with brain death, who were organ donors;
- Patients receiving renal replacement therapy at the time of ICU admission;
- Patients with AKI prior to ICU admission;
- Patients with AKI prior to Polymyxin B use.

Patients were divided into two groups: those who used the association of Polymyxin B + Vancomycin (Group I) and those who used only Polymyxin B (Group II). Demographical, clinical and laboratory parameters of the two groups were compared.

Treatment and drugs

Antimicrobial agents were selected by attendant physicians of the ICU and the hospital's Prevention and Control of Infections Commission based on clinical, laboratory and microbiologic parameters. None of the researchers interfered with drug choice. According to the institution's protocol, patients received a Polymyxin B daily dose of 25,000 IU/kg/day divided in two doses. Each 10,000 U equals 1 mg of Polymyxin B (Química Haller Ltda., Brazil). Vancomycin was administered in a dose of 30 mg/kg twice a day (Antibióticos do Brasil Ltda., Brazil). Serum Vancomycin concentration was not assessed due to laboratory scarce resources. Duration of Vancomycin use was not available in patient's charts. Both antibiotics were administered by intravenous route. Among other medications used by the patients during hospitalization, there were no other identifiable major nephrotoxins, such as contrast or aminoglycosides, or drugs with potential interactions with Polymyxin B or Vancomycin.

Studied parameters

The following parameters were investigated: Demographic data, comorbidities, outcomes (discharge, death) and death cause for those who did not survive; Signs and symptoms on hospital admission; Site of infection and etiologic agent; Laboratory evaluation on hospital and ICU admission, and during ICU stay, including serum creatinine, urea, electrolytes, hemoglobin, leucocytes, platelets, blood gas analysis, and calculated APACHE II score; Clinical parameters: use of vasoconstrictors, antihypertensive drugs, nonsteroidal anti-inflammatory and radiocontrast agents, as well as need of mechanical ventilation or hemodialysis, association with other antibiotics and estimated glomerular filtration rate (eGFR) by simplified MDRD equation (Modification of Diet in Renal Disease) [10].

Definitions

AKI was defined according to the RIFLE criteria [11]. Infection was defined according to the International Sepsis Forum criteria, and it was confirmed by attendant clinicians [12]. Oliguria was defined as urine output < 0.5 mL/kg/h in patients that had been effective hydrated. Dialysis was indicated to patients that remained oliguric after effective hydration or who presented fluid overload, in cases of uremia associated with hemorrhage or severe respiratory failure and when hyperkalemia or metabolic acidosis were refractory to clinical treatment.

Statistical analysis

Results were expressed through tables and mean ± standard deviation (SD). Statistical analysis was executed using SPSS for Windows version 20.0 (IBM, USA). Kolmogorov-Smirnov test was used to assess variable distribution. Categorical variables were analyzed using Pearson's Chi-square test, as appropriate. ANOVA test was used for categorical variables with three or more categories. Numeric variables were analyzed using Student's T test (for variables with normal distribution) or Mann–Whitney test (for variables with a non-normal distribution). Univariate analysis was performed for all variables in order to find risk factors for AKI. Variables with $p \leq 0.05$ were considered statistically significant and were included in the multivariate model. For the multivariate analysis we have considered AKI as the main outcome and included as possible risk factors those with significance in the univariate analysis. Regression logistic was then carried out with these variables, using a confidence interval (CI) = 95%.

Ethics

The study protocol was reviewed and approved by Ethics Committee of Fortaleza General Hospital. The Ethics Committee indicated that informed consent was not necessary because the study was retrospective, based only on chart review, with no individual identification of patients.

Results

A total of 158 ICU patients used Polymyxin B in the studied period. Forty-three patients were excluded because six of them used Polymyxin B for less than three days and 37 were performing hemodialysis before starting antibiotic treatment. Hence, 115 patients fulfilled the inclusion criteria. Among these, 59 (51.3%) used Polymyxin

B + Vancomycin (Group I) while 56 (48.7%) used only Polymyxin B (Group II).

Among these patients, 60 (52.2%) were males. Mean age was 59.2 ± 16.1 years. Systemic arterial hypertension was the most frequent comorbidity (55.6%), followed by heart failure (33.9%) and diabetes mellitus (26%). Hemodialysis was indicated for nine patients (7.82%). General mortality was 39.1%.

It was noted that patients in group I were significantly younger (56 ± 15 vs. 63 ± 16 years, $p = 0.03$) and presented a significantly lower incidence of pulmonary obstructive disease (6.7% vs. 19.6%; $p = 0.05$) and previous stroke (15.2 vs. 32.1%, $p = 0.047$). Duration of antimicrobial therapy (15 ± 6 vs. 14 ± 7 days, $p = 0.252$), and total accumulated Polymyxin B dose (18.1 ± 9.2 vs. 16.2 ± 12.3 million U, $p = 0.36$) were not significantly different between the two groups. In group I, 51 patients (86.4%) presented a Cumulative Polymyxin B dose > 10 million IU, while it happened in 40 patients (71.4%) from group II ($p = 0.06$). There were not significant differences in any other outcomes, demographical and clinical parameters, as summarized in Table 1.

The comparative analysis between the two groups also evidenced that group I presented a significantly higher estimated glomerular filtration rate (GFR) on ICU admission than group II (117.1 ± 70.5 vs. 91.5 ± 50 ml/min/1.73 m^2, $p = 0.02$). Group I also had lower levels of creatinine (0.9 ± 0.82 vs. 1.0 ± 0.59 mg/dL, $p = 0.014$) and urea (51.8 ± 23.7 vs. 94.5 ± 4.9 mg/dL, p=0.006) on ICU admission, as well as higher levels of hemoglobin (10.8 ± 1.5 vs. 10.0 ± 1.3 g/dL, $p = 0.016$) and platelets (339.4 ± 194.2 vs. 223.0 ± 121.6 10^3/mm^3, $p = 0.029$). The entire laboratory comparative analysis is presented in Table 2.

On the other hand, group I manifested a significantly higher incidence of AKI than group II (62.7% vs. 28.5%, $p = 0.005$). This result was confirmed even when stratified by RIFLE criteria ('Risk' 33.9% vs. 10.7%; 'Injury' 10.2% vs. 8.9%; 'Failure' 18.6% vs. 8.9%; $p = 0.03$), as shown in Table 3. In multivariate analysis, Vancomycin use in association with Polymyxin B did not increase the risk for AKI. On the other hand, accumulated Polymyxin B dose > 10 million IU was an independent predictor for AKI (OR = 2.72, 95% CI = 1.13 – 6.51, $p = 0.024$).

Table 1. Comparison of demographic data, comorbidities, treatment and outcomes between patients receiving Polymyxin B plus Vancomycin (Group I) or Polymyxin B alone (Group II).

	Group I ($N = 59$)	Group II ($N = 56$)	p
Age (years)	56 ± 15	63 ± 16	0.03
Age > 60 years	25 (42.3%)	35 (62.5%)	0.04
Gender			
Male	26 (44.1%)	34 (60.7%)	0.093
Female	33 (55.9%)	22 (39.3%)	
Comorbidities			
Hypertension	31 (52.5%)	33 (58.9%)	0.574
Heart Failure	22 (37.3%)	17 (30.3%)	0.434
Diabetes	13 (22%)	17 (30.3%)	0.396
Stroke	9 (15.2%)	18 (32.1%)	0.047
COPD	4 (6.7%)	11 (19.6%)	0.05
HIV	3 (5.0%)	1 (1.7%)	0.619
Treatment and outcomes			
Vasoconstrictors	35 (59.3)	36 (64.2%)	1.000
Mechanical Ventilation	57 (96.6%)	53 (94.6%)	0.674
NSAIDs	2 (3.4%)	3 (5.4%)	0.605
Time of treatment (days)	15 ± 6	14 ± 7	0.252
Accumulated Polymyxin B dose (million IU)	18.1 ± 9.2	16.2 ± 12.3	0.360
Dialysis	7 (11.8%)	2 (3.5%)	0.164
Deaths	22 (37.3%)	23 (41%)	0.706

Notes: COPD – Chronic obstructive pulmonary disease; NSAIDs – Nonsteroidal anti-inflammatory drugs. Student's t test, Mann-Whitney test and Chi-squared test were used. Variables were presented as mean ± SD. *P* values ≤ 0.05 were considered statistically significant.

Table 2. Comparison of laboratory data between patients receiving Polymyxin B plus Vancomycin (Group I) or Polymyxin B alone (Group II).

	Group I ($N = 59$)	Group II ($N = 56$)	p
eGFR (ml/min/1.73 m^2)	117.1 ± 70.5	91.5 ± 50	0.02
Cr (mg/dL)	0.9 ± 0.82	1.0 ± 0.59	0.014
Urea (mg/dL)	51.8 ± 23.7	94.5 ± 4.9	0.006
Hb (g/dL)	10.8 ± 1.5	10.0 ± 1.3	0.016
Leukocytes (10^3/mm^3)	13.3 ± 6.9	15.5 ± 7.2	0.323
Platelets (10^3/mm^3)	339.4 ± 194.2	223.0 ± 121.6	0.029
Na (mEq/L)	141 ± 10.1	142 ± 5.6	0.902
K (mEq/L)	3.2 ± 0.5	3.4 ± 0.6	0.283
HCO_3 (mEq/L)	22.5 ± 6.0	24.5 ± 4.7	0.396
APACHE II	13 ± 6	15 ± 7	0.293

Notes: GFR – estimated glomerular filtration rate; Cr – serum creatinine; Hb – hemoglobin; Na – serum sodium; K – serum potassium; HCO3 – serum bicarbonate; APACHE II – Acute physiology and chronic health evaluation II. Student's t test and Mann-Whitney test were used. Variables were presented as mean ± SD. *P* values ≤ 0.05 were considered statistically significant.

Table 3. AKI classification according to the RIFLE criteria among patients receiving Polymyxin B plus Vancomycin (Group I) or Polymyxin B alone (Group II).

	Group I ($N = 59$)	Group II ($N = 56$)	P
AKI	37 (62.7%)	16 (28.5%)	0.005
Risk	20 (33.9%)	6 (10.7%)	
Injury	6 (10.2%)	5 (8.9%)	0.03
Failure	11 (18.6%)	5 (8.9%)	

Notes: AKI – Acute kidney injury. Chi-squared test was used. *P* values ≤ 0.05 were considered statistically significant.

Discussion

This is the first study to compare the association of Vancomycin and Polymyxin B with isolated Polymyxin B use among critically ill patients in our region. The present study evidence that the association between Polymyxin B and Vancomycin potentiate nephrotoxicity and that cumulative Polymyxin B dose is an independent risk factor for AKI. Polymyxin B has been widely used as the last-resort treatment for ICU Gram-negative infected patients. Its nephrotoxicity seems to depend on dose, time of exposition and the presence of risk factors [5,13,14]. Its use has been associated to both higher

risk of developing AKI and increased 30 days mortality rates [15]. Polymyxin safety has been discussed in recent studies [16]. Host factors and comorbidities are important determinants of polymyxin nephrotoxicity and the magnitude of this toxicity uses to be mild to moderate [16]. Polymyxin nephrotoxicity is associated with d-aminobutyric acid contents and is similar to its effects on the outer bacterial membrane and it is dependent on drug concentration and exposure length. The antibiotic leads to membrane permeability increase, enhancing ions and water flow, causing edema and cell lysis [17]. Experimental studies shows renal tubular edema induced by polymyxin, and clinical studies evidences kidney disease manifested by glomerular filtration rate decrease and proteinuria, all events dependent on polymyxin cumulative dose [17]. New studies are under way aiming to develop less nephrotoxic synthetic antibiotics based on polymyxin [18].

Vancomycin is extensively used for Gram-positive severe infections, mostly due to methicillin-resistant *Staphylococcus aureus* (MRSA). The mechanism of its' nephrotoxicity are still poorly understood, but main theories state that it happens due to oxidative effects and changes in energy-dependent reabsorption function of the proximal tubule [19]. Vancomycin use may trigger AKI, especially when high doses are used for long periods. Also, its intermittent use is apparently more nephrotoxic than continuous intravenous infusion [20].

Due to the lack of new antimicrobial agents which are active against multidrug resistant bacteria (MDR), Polymyxin B + Vancomycin associations have been successfully tested *in vitro*. The synergic effects of these drugs derive from Polymyxin B action against Gram-negative bacterial membrane's integrity, leading to its disruption. In this case vancomycin can penetrate the bacteria's outer membrane and act on its targets in cell wall [21,22]. Furthermore, clinical use of the colistin-glycopeptide combination has been demonstrated to be a factor independently associated to better outcomes in severely ill patients, especially for those infected with MDR [23].

The comparison between the two groups (polymyxin in association with vancomycin or alone) evidenced a better clinical profile of the first group. Patients in group I were younger and presented significantly less comorbidities (stroke and pulmonary obstructive disease), so it was expected that they had a better outcome, but mortality was not different between the two groups. Regarding age, previous studies shows that advanced age is as an important risk factor for Polymyxin B renal toxicity [24,25]. Regarding renal function, group I presented a significantly better previous renal function than group II, with higher admission eGFR and lower admission urea and creatinine. Despite presenting more favorable previous clinical status and better renal function, patients in group I had a significant higher incidence of AKI, which reinforces the role of this antimicrobial synergy in nephrotoxicity, suggesting that the association between Polymyxin B and Vancomycin is nephrotoxic even for patients with low risk for developing AKI.

The synergic nephrotoxicity of these two drugs has been previously described. Concomitant administration of vancomycin to patients in a colistin-based antimicrobial treatment has been recognized as a risk factor for AKI [26,27]. Significant difference on AKI incidence was observed in our cohort. We hypothesized that vancomycin additional nephrotoxicity would be compensated by more favorable clinical profile, less comorbidities and better previous renal function in group I, but we were proven wrong. Even with higher GFR on admission, group I presented higher AKI incidence than group II, most likely due to concomitant Vancomycin use.

However, the role of Vancomycin co-administration for AKI development was not confirmed in multivariate analysis, since it was not an independent risk factor. This could be due to the small sample size. In fact, Vancomycin additional nephrotoxicity is still a matter of debate and at least one important study has questioned it [28]. Rocco et al. [28], in a large retrospective study, observed that the concomitant use of vancomycin and other nephrotoxic drugs with colistin did not increase the risk of AKI in ICU patients with normal baseline renal function, which was not observed in our study.

Furthermore, the only independent predictor of AKI in the present study was a cumulative Polymyxin B dose > 10 million IU. Interestingly, AKI was observed in our patients even using a smaller daily dose than that used in other studies [29,30]. Polymyxin B dose dependent nephrotoxicity is well described, and cumulative doses have been associated with higher incidence of AKI, similarly to the results in the present study [29,30].

In summary, we observed that patients receiving the association of Polymyxin B and Vancomycin had a higher incidence of AKI than those patients who used only Polymyxin B, despite presenting more favorable clinical profile and higher previous GFR. Cumulative Polymyxin B dose > 10 million IU was independently associated with AKI development.

Study limitations

Some of the study limitations are due to its retrospective nature and the small sample size. Since information was obtained from patient's records, some data were scarce or not available, such as duration of Vancomycin use. We did not have access to patients' data after ICU discharge, hence it was not possible to evaluate mortality and other outcomes after ICU stay. We also did not have vancomycin serum levels because it is not routine in the studied hospital.

It was not possible to assess serum Vancomycin levels due to scarce laboratory resources, which led to lack of precision about therapeutic Vancomycin doses. Also, some patients presented comorbidities which could affect renal function, but not in a very significant way, since normal previous creatinine level was an inclusion criterion of the study. Further prospective studies are then necessary to continue the investigation of Polymyxin and Vancomycin nephrotoxicity.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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