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Risk factors for acute kidney injury (AKI) in patients treated with polymyxin B and influence of AKI on mortality: a multicentre prospective cohort study

Maria Helena Rigatto[1], Tainá F. Behle[2], Diego R. Falci[3], Thiela Freitas[3], Natane T. Lopes[4], Mariá Nunes[4], Leonardo W. Costa[4] and Alexandre P. Zavascki[2,5]*

[1]*Infectious Diseases Service, Hospital São Lucas da Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil;* [2]*Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, 2350 Ramiro Barcelos St., Porto Alegre 90.035-903, Brazil;* [3]*Infection Control Service, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil;* [4]*Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;* [5]*Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul, Porto, Alegre, Brazil*

*Corresponding author. Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, 2350 Ramiro Barcelos St, Porto Alegre, 90.035-903, Brazil. Tel/Fax: +55 (51) 33598152; E-mail: azavascki@hcpa.ufrgs.br

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Objectives: The objectives of this study were to assess risk factors for acute kidney injury (AKI) in patients treated with polymyxin B, a last resort antibiotic against Gram-negative bacteria, with a focus on dose, and to determine the impact of AKI on mortality of these patients.

Methods: A multicentre prospective cohort study was performed including patients ≥18 years treated with intravenous polymyxin B for ≥48 h. The primary outcome was AKI defined by RIFLE criteria. Secondary outcomes were 30 day mortality and failure stage of AKI. Multivariate analysis with a Cox regression model was performed. The probability of developing AKI was determined in a logistic regression model.

Results: Four-hundred-and-ten patients were included. AKI occurred in 189 (46.1%) patients. Polymyxin B dose ≥150 mg/day was a risk factor for AKI: adjusted HR=1.95, 95% CI=1.31–2.89, P=0.01. Higher weight and age were also independently associated with AKI. The probability of developing AKI significantly increased with doses between 150 and 199 mg/day, regardless of patient weight, with no significant increase with higher doses. Higher weight also increased the risk in patients receiving the same daily doses. AKI was barely associated with increased risk for 30 day mortality (adjusted HR=1.35, 95% CI=0.99–1.85, P=0.06), while ≥150 mg/day did not increase this risk despite its association with AKI.

Conclusions: Polymyxin B total dose is highly related to the risk of AKI, regardless of patient weight. Thirty-day mortality tended to be higher in patients who developed AKI. The relationship between dose, AKI and mortality must be further investigated in studies specifically designed to evaluate this latter outcome.

Keywords: nephrotoxicity, colistin, PMB

Introduction

Infections caused by XDR Gram-negative bacteria are a growing problem worldwide, posing severe therapeutic challenges to clinicians.[1,2] Owing to the lack of new antibiotics, polymyxins (polymyxin B and colistin) have gained special importance in the last 15 years since they are the last-resort treatment against most infections by these organisms.[3–6] Nephrotoxicity, however, is the major adverse effect of these antibiotics, causing further difficulties in the management of these infections.[7–16]

Acute kidney injury (AKI) rates in patients receiving polymyxins range widely from 20% to 60%, even using standardized criteria such as RIFLE (Risk, Injury, Failure, Loss and End-stage renal disease) or AKIN (Acute Kidney Injury Network) to define AKI.[8–17] This broad range indicates that there are many determinants of these rates. Indeed, several risk factors have been identified, mostly in studies addressing colistin methanesulfonate (CMS)/colistin,[7,11–14] with fewer studies evaluating polymyxin B.[8,10,11,17] However, major differences in the pharmacokinetics (PK) of CMS/colistin and polymyxin B preclude direct extrapolation of clinical data from one study to another.[18,19] Additionally, previous studies were all retrospective and some included a limited number of patients, both factors impairing in-depth analysis of determinants of AKI in these patients.

Notably, dose, one of the most important risk factors for AKI,[7,8,10,12–14,17,18] was addressed in different ways in various studies. Most analysed calculated dose by mg (or international units)/kg,[7,8,13,14,18] while others considered actual received doses,[8,10,12,17] but the relationship between calculated dose and actual dose, along with some patient characteristics, such as baseline creatinine clearance and weight, have not been assessed. In addition, previous studies with polymyxin B evaluated risk factors for AKI in patients receiving adjusted doses for decreased creatinine clearance, a practice no longer recommended since total polymyxin B clearance is not affected by renal function.[19] This fact may potentially underestimate AKI rates and decrease the impact of dose on such an outcome.

Finally, it has been shown that minimal increases in creatinine are associated with worse outcomes, including mortality.[20] Nonetheless, the influence of AKI in patients receiving polymyxins, commonly for life-threatening infections, has not yet been investigated.

In this study, we aimed to evaluate risk factors for AKI in patients treated with polymyxin B, with particular emphasis on dose, and to assess the influence of developing this adverse event during therapy on mortality.

Patients and methods

Study design, settings and participants

This was a multicentre prospective cohort study performed at three tertiary-care teaching hospitals in Porto Alegre, Brazil. All patients aged ≥18 years who received intravenous polymyxin B from 1 February 2013 to 31 January 2014 were eligible for the cohort. Patients were excluded if they received polymyxin B for a period <48 h, were on renal replacement therapy, had a creatinine clearance ≤10 mL/min at the beginning of polymyxin B therapy or did not have serum creatinine collected after the beginning of polymyxin B therapy. In patients who received more than one treatment with polymyxin B, only the first course was analysed. Therapy was at the discretion of the attendant physician. Institutional protocols recommended doses of 1.5–3.0 mg/kg/day in two divided administrations. Loading doses and dose adjustment according to creatinine clearance were not recommended. The study was approved by the local ethics committee of each hospital, which waived the need to obtain informed consent.

Variables and definitions

The primary outcome was the development of AKI during treatment with polymyxin B, assessed by RIFLE criteria.[21] Baseline creatinine was that measured on the day that polymyxin B was initiated. Secondary outcomes were 30 day mortality and the development of renal failure by RIFLE. Subgroup analyses, *a priori* defined, were performed in patients who had and had not been admitted to an ICU at the beginning of therapy and in those with baseline creatinine clearance above and below 60 mL/min.

Variables potentially related to AKI were assessed, including: age; gender; weight; BMI; baseline creatinine clearance (estimated by Cockcroft–Gault formula); Charlson comorbidity score[22] and the presence of specific comorbid conditions associated with AKI, such as diabetes and cardiovascular disease; the use of other nephrotoxic drugs or nephrotoxic contrast before the development of AKI; ICU admission; and the use of vasoactive drugs and mechanical ventilation at the beginning of polymyxin B therapy.

Dosages were evaluated as the average daily dose of polymyxin B (sum of total daily dose each day divided by the number of days until the outcome: development of any degree of AKI or the end of therapy for those who had not developed AKI) and daily dose by mg/kg/day. Average daily doses were further categorized as ≥150 and ≥200 mg/day, according to the incidence of AKI in each dose group (see below) and to the finding of a previous study.[17]

Statistical analysis

All of the statistical analysis was carried out using SPSS for Windows, version 18.0. Bivariate analysis was performed separately for each of the variables. *P* values were calculated using the χ^2 or Fisher's exact test for categorical variables and the Student's *t*-test or the Wilcoxon rank-sum test for continuous variables. Covariates were compared between patients that developed or not any degree of AKI by the RIFLE criteria; those with a *P* value ≤0.2 were included in a Cox proportional hazards model in a forward stepwise regression. Variables were checked for confounding and collinearity. Variables with a *P* value ≤0.10 were retained in the model. Death and end of polymyxin B therapy were the censoring events in the Cox regression model. The probability of presenting any AKI according to the dose of polymyxin B was determined in a logistic regression model, including all variables of the final Cox regression model.

To evaluate the effect of AKI on 30 day mortality, a Cox proportional hazards model was performed, including variables with a *P* value ≤0.2 in bivariate analysis for the outcome. Bivariate and multivariate analysis was also performed to assess risk factors for renal failure by RIFLE.

The proportional hazards assumption was graphically checked by inspecting the log[−log(*S*)] plot. Tests for interactions were not performed. All tests were two-tailed and a *P* value ≤0.05 was considered significant.

Results

A total of 686 patients received polymyxin B during the study period. Of these, 276 were excluded, resulting in a total of 410 patients included for analyses (Figure 1). The mean age of patients was 64.0 ± 16.9 years, 58.7% were male and their mean weight was 66.2 ± 16.2 kg. The presumed or confirmed sites of infection were: respiratory tract (264, 64.4%); bloodstream (47, 11.5%); urinary tract (45, 11.0%); abdominal (31, 7.6%); skin and soft tissue (11, 2.7%); other sites (20, 4.9%); and sepsis without a defined primary site (28, 6.8%). Two-hundred-and-forty-seven (60.2%) patients had bacterial isolates recovered in cultures requested by the attendant physician; the remaining 163 (39.8%) had negative culture results or this exam was not requested. The most commonly recovered bacterium was *Acinetobacter baumannii* (150, 60.7%), followed by *Pseudomonas aeruginosa* (45, 18.2%), *Klebsiella pneumoniae* (42, 17.0%), *Escherichia coli* (5, 2.0%) and *Enterobacter aerogenes* (5, 2.0%). The mean polymyxin B daily dose was 2.4 ± 0.69 mg/kg and the median average daily dose was 150 mg (IQR = 140–187). The follow-up of patients under treatment with polymyxin B ranged from 2 to 45 days.

Any degree of AKI occurred in 189 (46.1%) patients. Of these, 92 (48.7%) were classified as Risk; 45 (23.8%) as Injury; and 52 (27.5%) as Failure. The median time to develop AKI was 6 days (IQR = 3–10). The incidence of AKI according to median average daily dose was 32.0% (33 of 103) of patients receiving <150 mg, 54.0% (109 of 202) of those receiving 150–199 mg and 44.8% (47 of 105) of those receiving ≥200 mg, *P* = 0.001. The incidence of AKI did not significantly differ among different categories of doses by mg/kg: 53 (28.0%) with <2 mg/kg/day; 57 (30.2%) with 2–2.49 mg/kg/day; 52 (27.0%) with 2.5–2.99 mg/kg/day; and 28 (14.8%) with ≥3 mg/kg/day (*P* = 0.16). The mean ± SD doses (mg/kg/day) according to RIFLE classes were: no AKI = 2.48 ± 0.70; Risk = 2.36 ± 0.72; Injury = 2.30 ± 0.65; and Failure = 2.42 ± 0.62 (*P* = 0.31).

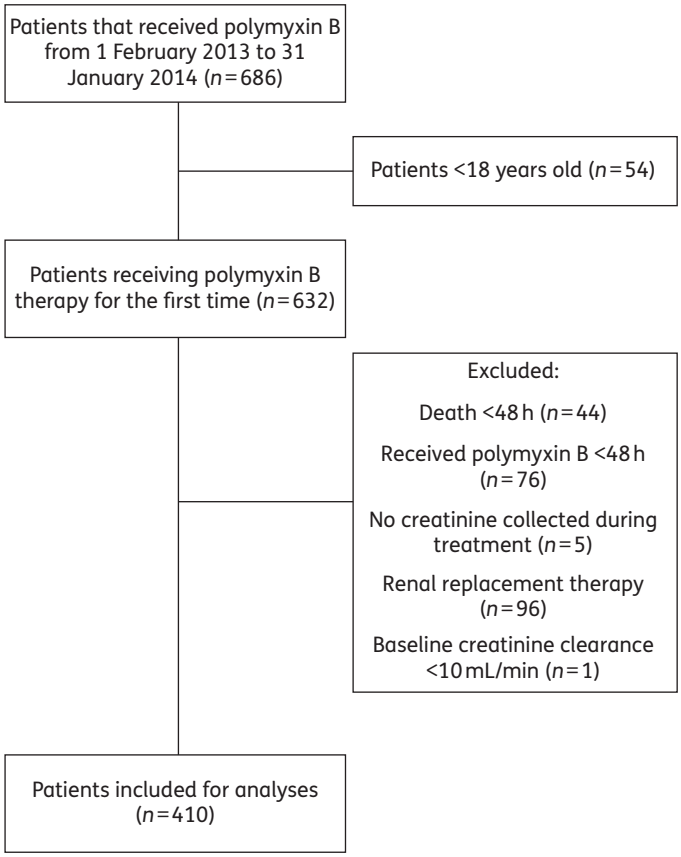

Figure 1. Flow chart of number of eligible and excluded patients.

The bivariate analysis for AKI is shown in Table 1. In multivariate analysis, polymyxin B dose ≥150 mg/day was an independent risk factor for AKI, as were older age and higher weight (Table 2). Changing weight for BMI or adding polymyxin B daily dose in mg/kg/day did not significantly change the final results. The predicted probability of developing any degree of AKI, according to polymyxin B dose and weight, is shown in Figure 2.

Subgroup analysis

Of the 222 patients in the ICU, 111 (50.0%) developed AKI. Polymyxin B dose ≥150 mg/day was independently associated with AKI: HR=3.42, 95% CI=1.58–7.43, *P*=0.002, adjusting for the same variables that remained in the main model. Of the 188 patients outside the ICU, AKI occurred in 78 (41.5%). Polymyxin B dose ≥150 mg/day presented a trend towards association with AKI (HR=1.65, 95% CI=0.99–2.75, *P*=0.054).

Two-hundred-and-twenty patients had a baseline creatinine clearance <60 mL/min: 98 (44.6%) developed AKI. Polymyxin B dose ≥150 mg/day was independently associated with AKI (HR=2.51, 95% CI=1.45–4.36, *P*=0.001). In patients (*n*=190) with baseline creatinine clearance ≥60 mL/min, 91 (47.9%) developed AKI. Dose ≥150 mg/day was not significantly associated with an increased risk for AKI (HR=1.38, 95% CI=0.78–2.43, *P*=0.27).

Secondary outcomes

The 30 day mortality rate was 42.0% (172 of 410). The development of AKI was significantly associated with 30 day mortality: 52.3% (90 of 172) versus 41.6% (99 of 238), *P*=0.04. Age (*P*<0.001), ICU admission (*P*<0.001), mechanical ventilation (*P*<0.001), the use of vasoactive drugs (*P*<0.001), Charlson comorbidity index (*P*=0.001), lower baseline creatinine clearance (*P*=0.001) and polymyxin B dose (*P*=0.158) were also potentially related to 30 day mortality in bivariate analysis and were evaluated in a Cox regression model (Table 3).

Fifty-two (12.7%) of 410 patients developed Failure by RIFLE. Time to develop failure was 6.5 (IQR=3–12) days. The incidence of failure was 1.7% (2 of 115) of patients receiving <150 mg/day, 16.8% (33 of 196) of those receiving 150–199 mg/day and 17.2% (17 of 99) of those receiving ≥200 mg/day, *P*<0.001.

Table 1. Potential risk factors for AKI

Variable	AKI (*n*=189)	No AKI (*n*=221)	*P*
Age (years)	66.7±15.3	61.7±17.9	0.03
Male	108 (57.1)	132 (59.7)	0.67
Weight (kg)	68.7±15.7	64.0±16.3	0.03
BMI (kg/m^2)	24.8±5.3	23.4±5.8	0.01
Baseline creatinine clearance (mL/min)	68.9±48.7	69.0±45.6	0.32
Cardiovascular disease	123 (65.1)	116 (52.5)	0.01
Diabetes mellitus	41 (21.7)	49 (22.2)	0.99
Charlson score	2 (1–4)	2 (1–6)	0.03
Other nephrotoxic drugs	123 (65.1)	153 (69.2)	0.37
Vancomycin	91 (48.1)	107 (48.4)	0.99
Aminoglycoside	15 (7.9)	22 (10.0)	0.59
Furosemide	58 (30.7)	71 (32.1)	0.84
Non-steroidal anti-inflammatory drugs	0	2 (0.9)	0.50
Amphotericin B	5 (2.6)	2 (0.9)	0.26
Aciclovir/ganciclovir	8 (4.2)	14 (6.3)	0.47
Use of nephrotoxic contrast	21 (11.1)	24 (10.9)	0.99
Vasoactive drugs	53 (28.0)	54 (24.4)	0.47
ICU admission	111 (58.7)	111 (50.2)	0.11
Mechanical ventilation	85 (45.0)	86 (38.9)	0.25
Polymyxin B daily dose (mg)	160.1±36.2	154.7±40.7	0.16
Polymyxin B (mg/kg/day)	2.4±0.67	2.5±0.70	0.09
Polymyxin B dose ≥150 mg/day	156 (82.5)	151 (68.3)	0.001
Polymyxin B dose ≥200 mg/day	47 (24.9)	59 (26.7)	0.76

Data are presented as *n* (%), mean±SD or median (IQR).

Table 2. Cox proportional hazards regression model for AKI

Variable[a]	HR (95% CI)	*P*
Polymyxin B dose ≥150 mg/day	1.95 (1.31–2.89)	0.001
Age (years)	1.02 (1.01–1.03)	0.01
Weight (kg)	1.01 (1.00–1.02)	0.04
ICU admission	1.09 (0.81–1.47)	0.57
Baseline creatinine clearance (mL/min)	1.00 (1.00–1.01)	0.63

[a]Baseline creatinine clearance and ICU were forced into this model for adjustment of potential residual confounding.

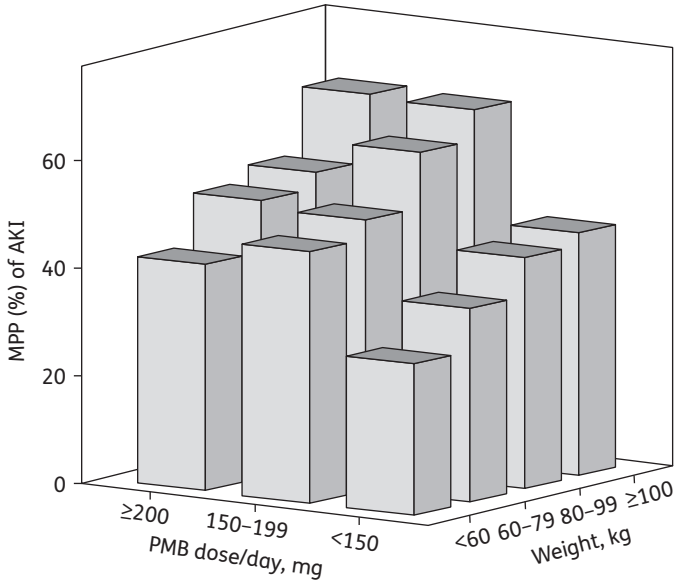

Figure 2. Mean predicted probability (MPP) of developing AKI according to polymyxin B (PMB) dose and weight as determined by a logistic regression model adjusting for dose, weight, age, baseline creatinine clearance and ICU admission. The MPP of AKI significantly increased (two-way ANOVA) in patients with PMB doses ≥150 mg ($P<0.0001$) and with higher weight ($P<0.0001$); MPP tended to increase in higher weight patients receiving doses ≥150 mg ($P=0.11$). The MPP of AKI ± SD according to weight and dose were: <60 kg, <150 mg = 28.1% ± 9.8% ($n=55$), 150–199 mg = 46.7% ± 8.9% ($n=68$) and ≥200 mg = 42.0% ± 10.4% ($n=17$); 60–79 kg, <150 mg = 35.9% ± 9.1% ($n=40$), 150–199 mg = 49.9% ± 9.1% ($n=105$) and ≥200 mg = 51.4% ± 8.1% ($n=57$); 80–99 kg, <150 mg = 42.8% ± 6.9% ($n=7$), 150–199 mg = 60.1% ± 7.5% ($n=21$) and ≥200 mg = 54.1% ± 11.6% ($n=25$); and ≥100 kg, <150 mg = 45.0% ± 21.5% ($n=2$), 150–199 mg = 65.6% ± 11.1% ($n=5$) and ≥200 mg = 65.8% ± 11.4% ($n=8$).

Table 3. Cox proportional hazards regression model for renal failure, according to RIFLE criteria

Variable[a]	HR (95% CI)	*P*
Polymyxin B dose ≥150 mg/day	9.81 (2.37–40.62)	0.002
Age (years)	1.00 (0.98–1.02)	0.85
Weight (kg)	1.03 (1.01–1.04)	0.001
ICU admission	1.36 (0.75–2.44)	0.31
Baseline creatinine clearance (mL/min)	0.99 (0.99–1.00)	0.14

[a]Baseline creatinine clearance and ICU were forced into this model for adjustment of potential residual confounding.

Factors potentially related to failure in bivariate analysis were polymyxin B dose ≥150 mg/day ($P<0.001$), polymyxin median daily dose ($P=0.001$), weight ($P=0.002$), mechanical ventilation ($P=0.008$), ICU admission ($P=0.059$), BMI ($P=0.094$), use of vasoactive drugs ($P=0.184$), age ($P=0.187$) and polymyxin B dose ≥200 mg/day ($P=0.187$). In multivariate analysis, polymyxin B dose ≥150 mg was strongly associated with development of failure, along with higher weight (Table 4). The predicted probability of developing failure, according to polymyxin B dose and weight, is shown in Figure 3.

Table 4. Cox proportional hazards regression model for 30 day mortality

Variable	HR (95% CI)	*P*
AKI	1.35 (0.99–1.85)	0.06
Dose ≥150 mg/day	0.74 (0.51–1.07)	0.11
Vasoactive drug	1.58 (1.10–2.27)	0.01
ICU admission	1.70 (1.16–2.50)	0.01
Baseline creatinine clearance (mL/min)	0.99 (0.98–0.99)	0.001
Charlson	1.10 (1.04–1.17)	0.002
Age (years)	1.01 (1.00–1.02)	0.19

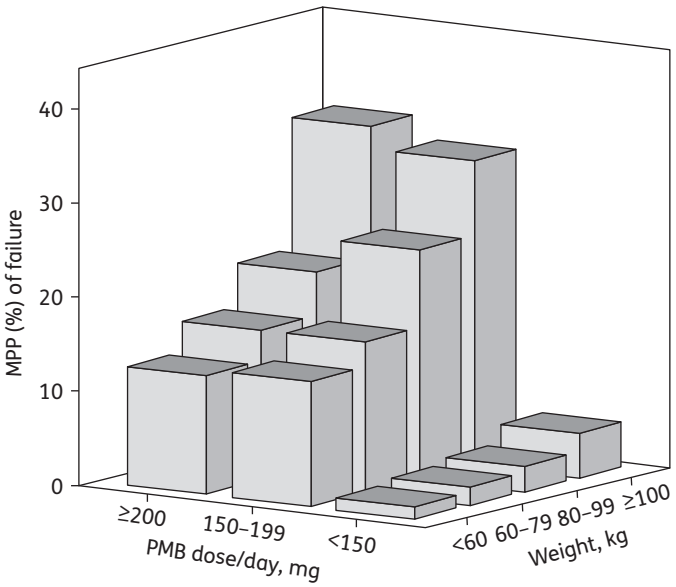

Figure 3. MPP of developing Failure by RIFLE[21] criteria, according to PMB dose and weight, as determined by a logistic regression model adjusting for dose, weight, age, baseline creatinine clearance and ICU admission. The MPP of Failure significantly increased (two-way ANOVA) in patients with polymyxin B doses ≥150 mg ($P<0.0001$) and with higher weight ($P<0.0001$); MPP (%) of failure significantly increased in higher-weight patients receiving doses ≥150 mg ($P<0.0001$). The MPP of failure ± SD according to weight and dose were: <60 kg, <150 mg = 1.3% ± 0.3% ($n=58$), 150–199 mg = 13.3% ± 3.1% ($n=65$) and ≥200 mg = 12.5% ± 2.5% ($n=17$); 60–79 kg, <150 mg = 2.0% ± 0.6% (n = 44), 150–199 mg = 16.0% ± 3.9% ($n=104$) and ≥200 mg = 16.0% ± 4.4% ($n=54$); 80–99 kg, <150 mg = 2.8% ± 0.6% ($n=9$), 150–199 mg = 24.4% ± 3.9% ($n=22$) and ≥200 mg = 20.7% ± 4.7% ($n=22$); and ≥100 kg, <150 mg = 4.8% ± 1.6% ($n=3$), 150–199 mg = 32.4% ± 5.9% ($n=5$) and ≥200 mg = 34.7% ± 11.8% ($n=7$).

Discussion

Our study showed that polymyxin B dose ≥150 mg/day was associated with higher risk of developing any degree of AKI and renal failure regardless of patient weight, which was also an independent risk factor. This risk did not significantly increase with doses ≥200 mg/day. It was also demonstrated that the development of AKI tended to increase 30 day mortality rates.

The finding that polymyxin B dose ≥150 mg/day significantly increased the risk of AKI by ∼2-fold regardless of patient weight is of paramount importance, since it may have major clinical implications and also contributes to understanding of the mechanisms of renal damage by polymyxins. The predicted probability determined by the logistic regression model corroborates the findings of the Cox regression analysis and both suggest that there might be a total daily dose toxicity threshold (150 mg/day in our study), since the higher AKI rates with doses equal to or above this threshold were not dependent on the patient's weight and did not significantly increase if the dose was further augmented. Previous studies using standardized criteria have also described a significant effect of high-dose regimens on the development of AKI,[8,10] but none has analysed total daily dose adjusted for patient weight.

Our findings are in accordance with experimental results showing that the kidney damage results from the accumulation of polymyxin B in the organ owing to high reabsorption rates of this drug, notably by the proximal tubular cells in the renal cortex.[23,24] Additionally, it has been shown that tubular reabsorption of polymyxin B seems to be a saturable non-passive mechanism.[18] In other words, proximal tubular cells have a limited capacity for polymyxin B reabsorption; thus, polymyxin B concentrations above the threshold reabsorption capacity of tubular cells would be reabsorbed at lower rates, resulting in a decreased additional toxicity.

The hypothesis of a more 'toxic polymyxin B dose threshold' is also supported by the remarkably low incidence of renal failure, which is supposed to be determined by a greater extent of kidney damage, in patients receiving daily doses <150 mg (1.7%), regardless of patient weight. It is important to consider, however, that this specific total daily dose threshold of 150 mg may only be valid if polymyxin B is administered in two split doses over a 1–4 h infusion (infusion durations in our study), because more fractionated or continuous infusions of polymyxin B result in higher accumulation of this antibiotic in the kidney,[18] potentially determining higher AKI rates.

Another important finding of our study was that patients developing any degree of AKI had higher risk of 30 day mortality. Previously, only higher crude mortality rates in patients who develop AKI have been reported.[10,14,17] However, despite the association of polymyxin B dose ≥150 mg/day with increased risk of AKI and the fact that patients who developed AKI had higher mortality rates, in the multivariate model, patients receiving a dose ≥150 mg/day showed a slight tendency to have lower 30 day mortality rates. This suggests that the benefit of receiving higher doses may overcome the risk of developing AKI. A protective effect of dose on mortality regardless of the development of AKI has previously been found in a retrospective study.[17] This finding may be explained by the fact that these higher doses will result in higher AUC and, since free AUC/MIC is the PK/pharmacodynamic (PD) index that best predicts polymyxins activity, these patients would be more likely to have polymyxin B blood concentrations nearer to the PK/PD target.[19] In fact, since polymyxin B clearance is not dependent on creatinine clearance, dose adjustment for decreased creatinine clearance will result in lower AUC, potentially resulting in worse outcomes. Nevertheless, it should be noted that this study was not designed to assess the impact of dose, either as total dose or as mg/kg, on mortality rates, but only to evaluate if the dose associated with an increased risk of AKI also results in higher mortality. Some important variables that might affect 30 day mortality, such as combination therapy, time to appropriate therapy and antibiotic susceptibility, among others, were not evaluated; thus, we prefer a more conservative interpretation of these results, stating that, despite the increased risk for AKI, polymyxin B dose ≥150 mg/day was at least not harmful at 30 days.

In our study, higher weight was also independently associated with increased risk of AKI. This finding has also been previously reported with polymyxin B[8] and CMS/colistin.[14] However, our findings indicate that the association of weight with AKI is not dependent on the dose administered. Interestingly, the probability of any degree of AKI or failure in patients receiving a dose ≥150 mg/day of polymyxin B was increased in patients with higher weight. The reasons for this increased risk of AKI in patients with higher weight require further investigation since it is not dose dependent.

Older age is a known risk factor for AKI[20] that has also been found in previous studies with polymyxin B and CMS/colistin.[11,14,17,25] In the subgroup of patients with creatinine clearance <60 mL/min, the effect of dose on AKI was stronger than in patients with higher creatinine clearance. Considering that doses should not be adjusted according to renal function, it is expected that patients with previous renal impairment may be more susceptible to developing further injury. Finally, the more marked effect of dose observed in patients in the ICU may be explained by an increased likelihood for the presence of other factors affecting renal function that might not be fully captured by the variables analysed.

Our study was limited by the lack of PK evaluation. Nonetheless, considering that our findings about doses were based on analysis that considered patient weight, a covariate that has been shown to affect polymyxin B total body clearance,[19] we believe that this limitation does not preclude our conclusions. Nonetheless, it may be important in future studies addressing the effect of weight on the risk of AKI. We also did not exclude patients with worsening renal function prior to polymyxin B therapy. However, if this had occurred, there is no particular reason to believe that it might have occurred differently in different dosage groups; moreover, the inclusion of baseline creatinine clearance in the model is likely to have adjusted for any confounding effect of such a non-measured potential event.

In conclusion, we present findings of major importance for the clinical management of patients treated with polymyxin B: nephrotoxicity depends on total daily dose regardless of patient weight. Higher risk for AKI was observed with total daily doses between 150 and 199 mg, with no significant increase with higher total daily doses. Baseline characteristics of the patients, such as age and, notably, weight, significantly increased the risk of AKI. Additionally, developing any degree of AKI during treatment with polymyxin B increased the risk of overall mortality, but the doses determining increased risk for AKI did not increase this risk and may even be a protective factor. Further studies are necessary to evaluate the impact of dose on mortality considering the effect of AKI on this outcome.

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Transparency declarations

None to declare.

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