Multicenter Prospective Cohort Study of Renal Failure in Patients Treated with Colistin versus Polymyxin B

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Nephrotoxicity is the main adverse effect of colistin and polymyxin B (PMB). It is not clear whether these two antibiotics are associated with different nephrotoxicity rates. We compared the incidences of renal failure (RF) in patients treated with colistimethate sodium (CMS) or PMB for ≥ 48 h. A multicenter prospective cohort study was performed that included patients aged ≥ 18 years. The primary outcome was renal failure (RF) according to Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) criteria. Multivariate analysis with a Cox regression model was performed. A total of 491 patients were included: 81 in the CMS group and 410 in the PMB group. The mean daily doses in milligrams per kilogram of body weight were 4.2 ± 1.3 and 2.4 ± 0.73 of colistin base activity and PMB, respectively. The overall incidence of RF was 16.9% (83 patients): 38.3% and 12.7% in the CMS and PMB groups, respectively ($P < 0.001$). In multivariate analysis, CMS therapy was an independent risk factor for RF (hazard ratio, 3.35; 95% confidence interval, 2.05 to 5.48; $P < 0.001$) along with intensive care unit admission, higher weight, older age, and bloodstream and intraabdominal infections. CMS was also independently associated with a higher risk of RF in various subgroup analyses. The incidence of RF was higher in the CMS group regardless of the patient baseline creatinine clearance. The development of RF during therapy was not associated with 30-day mortality in multivariate analysis. CMS was associated with significantly higher rates of RF than those of PMB. Further studies are required to confirm our findings in other patient populations.

Extensively drug-resistant Gram-negative bacteria (XDR-GNB) are a major public health concern worldwide and pose a challenge to current antimicrobial therapy. Polymyxins B and E (colistin) have reemerged as agents of last resort to treat infections caused by XDR-GNB (1), but despite treatment with these drugs, mortality is usually high (2–4).

Nephrotoxicity is the most common adverse effect of polymyxins, with rates of acute kidney injury (AKI) ranging from 20% to 60% according to recent studies using standardized criteria to evaluate nephrotoxicity (5–10). The development of AKI during polymyxin therapy has been associated with an even worse prognosis for patients with XDR-GNB infections (2, 10–12). Therefore, it is important to determine whether different polymyxins have different nephrotoxicity profiles in the clinical context.

The use of colistin, administered as colistimethate sodium (CMS), is more frequent worldwide, whereas polymyxin B (PMB) is prescribed mainly in some parts of the United States, Brazil, Malaysia, India, and Singapore (1). While recent studies have suggested that CMS may be more nephrotoxic than PMB (5, 9), other investigations have not found significant differences in nephrotoxicity between these drugs (10, 13). However, because other factors may play a role in AKI at early stages (risk or injury stages of the Risk, Injury, Failure, Loss, and End-stage renal disease [RIFLE] classification) (14), highly distinct nephrotoxicity rates have been reported (5, 9, 10), and the issue remains unresolved.

The failure class of RIFLE is less susceptible to being affected by other factors that can determine minor kidney damage, and the

impact on clinical outcomes is also higher as the degree of AKI by RIFLE increases (15, 16). Therefore, it may be expected that the failure class would be more specific for reflecting an injury caused by exposure to a nephrotoxic agent. In this study, we compare the rates of renal failure (RF), defined by RIFLE criteria, that are associated with CMS and PMB treatment.

MATERIALS AND METHODS

Study design, settings, and participants. This was a multicenter prospective cohort study that was performed at six tertiary care teaching hospitals in Brazil. CMS was used in three of these hospitals (2,096, 600, and 313 beds), and PMB was used in the other three hospitals (843, 801, and 661 beds). A study with this group of PMB-treated patients has been previously published (12). Patients who were ≥ 18 years of age and who were receiving intravenous CMS or PMB from 1 February 2013 to 31 January

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2014 were eligible for inclusion. Exclusion criteria included the following: polymyxin treatment for <48 h, creatinine clearance of ≤ 10 ml/min (estimated by the Cockcroft-Gault equation based on actual body weight) or renal replacement therapy at the beginning of polymyxin therapy, treatment with polymyxins prior to the start of the study, or absence of follow-up evaluation of serum creatinine. Only the first course of polymyxin treatment was considered.

Therapy management was at the discretion of the attending physician. Loading doses and dose adjustment according to creatinine clearance were recommended only for CMS (17, 18). Institutional protocols recommended the use of colistin base activity (CBA)-transformed CMS doses, including loading doses, as suggested in a recent study (17), of $5 \times$ actual body weight and maintenance doses (12 or 24 h after loading dose) of $2.5 \times (1.5 + \text{creatinine clearance} + 30)/\text{day}$ every 12 or 8 h. Caution was recommended for loading doses exceeding 10 million IU/day, but no dose capping was imposed. Recommended PMB doses were 1.5 to 3 mg/kg (based on actual body weight) per day administered every 12 h. All hospitals used the same polymyxin brands, including Colis-Tek for CMS (Opem Pharmaceuticals; 1 mg of CBA or $\sim 30,000$ IU of CMS) and Sulfato de Polimixina B (Eurofarma, Brazil) for PMB. The study was approved by the ethics committee at each hospital, which waived the need to obtain informed consent.

Variables and definitions. The primary outcome was the development of RF defined according to RIFLE criteria (F class) as a 3-fold increase in baseline creatinine or a 75% decrease in estimated baseline serum creatinine clearance (estimated by the Cockcroft-Gault formula) or creatinine of ≥ 4 mg/dl with an acute rise of 0.5 mg/dl over 48 h during treatment with polymyxins (14). Thirty-day mortality was a secondary outcome. The potential contribution of the following variables to RF was analyzed: age, gender, weight, body mass index, Charlson comorbidity index (19) and the presence of specific comorbid conditions associated with AKI (diabetes and cardiovascular disease), concomitant use of other nephrotoxic drugs for at least 48 h or nephrotoxic contrast before the development of RF, site of infection according to CDC criteria (20), intensive care unit (ICU) admission, and use of vasoactive drugs initiated in the first 24 h of polymyxin therapy. Acute physiology and chronic health evaluation II (APACHE II) (21) score at the time of polymyxin treatment initiation was evaluated only in patients admitted to the ICU. Doses expressed as mean daily doses (sum of total daily doses divided by the number of days until the event—RF—or until the end of therapy) and as milligrams per kilogram per day (based on actual body weight) were evaluated.

Statistical analysis. All statistical analyses were carried out using SPSS for Windows, version 18.0.

P values were calculated using the χ^2 or Fisher's exact test for categorical variables and the Student *t* test or the Wilcoxon rank sum test for continuous variables in bivariate analysis. Covariates were compared in CMS versus PMB and in patients who developed renal failure versus patients who did not develop renal failure. For the secondary outcome, covariates were compared in survivors versus nonsurvivors at 30 days. Variables with *P* values of ≤ 0.2 were included in a Cox proportional hazards model in forward stepwise regression. Variables with *P* values of ≤ 0.10 were maintained in the model. Proportional hazards assumption was graphically checked by inspecting the $\log[-\log(S)]$ plot. All tests were two-tailed. A *P* value of ≤ 0.05 was considered significant. A subgroup analysis was performed for ICU and non-ICU patients, for patients with glomerular filtration rates (GFRs) of ≥ 60 ml/min or < 60 ml/min, and for patients receiving high doses of CBA (≥ 300 mg/day) and PMB (≥ 150 mg/day), controlling for the same variables of the main multivariate model. Thirty-day mortality was evaluated in a Cox regression model controlled for variables that differed between the two drugs using the same inclusion and exclusion criteria used in the main model.

TABLE 1 Characteristics of colistimethate sodium and polymyxin B groups

Variable ^a	CMS (<i>n</i> = 81)	PMB (<i>n</i> = 410)	<i>P</i> value
Gender, male	56 (69.1)	240 (58.5)	0.097
Age, yr	52.2 $\pm$ 17.8	64.0 $\pm$ 16.9	<0.001
Weight, kg	70.8 $\pm$ 13.5	66.2 $\pm$ 16.2	0.07
Body mass index	25.2 $\pm$ 4.0	24.0 $\pm$ 5.6	0.024
Baseline creatinine clearance, ml/min ^b	93.1 $\pm$ 65.4	69.0 $\pm$ 47.0	0.002
Infection site			
Respiratory	40 (49.4)	266 (64.9)	0.012
Bloodstream	8 (9.9)	46 (11.2)	0.874
Urinary tract	4 (4.9)	45 (11.0)	0.108
Abdominal	3 (3.7)	30 (7.3)	0.332
Other	26 (32.1)	52 (12.7)	0.001
Other nephrotoxic drug	68 (84.0)	294 (71.7)	0.032
Aminoglycoside	10 (12.3)	38 (9.3)	0.517
Vancomycin	48 (59.3)	198 (48.3)	0.093
NSAID ^c	1 (1.2)	2 (0.5)	0.418
Furosemide	32 (39.5)	132 (32.2)	0.252
Amphotericin B	0	7 (1.7)	0.606
Acyclovir/ganciclovir	11 (13.6)	22 (5.4)	0.014
Nephrotoxic contrast	7 (8.6)	45 (11.0)	0.670
Microbiologically confirmed infection	53 (65.4)	248 (60.5)	0.478
Vasoactive drug	25 (30.9)	107 (26.1)	0.455
ICU admission	59 (72.8)	22 (54.1)	0.003
Cardiovascular disease	16 (19.8)	239 (58.3)	<0.001
Diabetes	11 (13.6)	90 (22.0)	0.120
Charlson	1 (0–2)	2 (1–5)	<0.001

^a Data are presented as number (%), mean $\pm$ SD, or median (interquartile range).

^b Range of CMS, 12.0 to 279, and of PMB, 11.1 to 315.9 ml/min.

^c NSAID, nonsteroidal anti-inflammatory drugs.

RESULTS

A total of 794 patients were eligible for the study; 108 received CMS, and 686 received PMB. Twenty-seven and 276 were excluded from the CMS and PMB groups, respectively, resulting in 81 patients receiving CMS and 410 receiving polymyxin B for the analysis. The sites of infection were the respiratory tract in 306 (62.3%) patients, bloodstream in 54 (11.0%) patients, urinary tract in 49 (10.0%) patients, intraabdominal in 33 (6.7%) patients, and other sites in 81 (16.5%) patients. The most frequent pathogen was *Acinetobacter baumannii* (180 isolates, 59.8%) followed by *Klebsiella pneumoniae* (55, 18.3%), *Pseudomonas aeruginosa* (51, 16.9%), *Enterobacter* spp. (9, 3.0%), and *Escherichia coli* (5, 1.7%). In 190 (38.7%) patients, infection site samples yielded no bacterial growth. The characteristics of each group are described in Table 1.

The mean and median estimated creatinine clearance of the entire cohort was 72.9 ± 51.2 ml/min (ranging from 11.1 to 315.9) and 59.9 ml/min (interquartile range [IQR], 37.1 to 92.6). The mean milligram per kilogram per day dose was 4.2 ± 1.3 for CBA and 2.4 ± 0.7 for PMB. The median total daily dose was 300 mg (IQR, 253 to 300) for CBA and 150 mg (IQR, 140 to 187) for PMB. All patients in the CMS group received the drug every 12 or 8 h, and all PMB-treated patients received the drug every 12 h. Fifty-

FIG 1 Incidence of renal failure (RF) in colistimethate sodium (CMS)-treated (black) and polymyxin B (PMB)-treated (gray) patients in distinct categories of baseline creatinine clearance. Incidences of RF in CMS and PMB groups were, respectively, 39.3% (11/28 patients) and 7.9% (8/101) in patients with creatinine clearances of ≥ 90 ml/min ($P < 0.001$), 32.0% (8/25) and 18.7% (17/91) in patients with creatinine clearances between 60 and 89 ml/min ($P = 0.25$), 44.4% (8/18) and 7.9% (11/139) in patients with creatinine clearances between 30 and 59 ml/min ($P < 0.001$), and 37.5% (3/8) and 20.3% (16/79) in patients with creatinine clearances of < 30 ml/min ($P = 0.36$). Mean daily doses $\pm$ standard deviation (SD) (mg) of colistin base activity (black circles) were 318.4 ± 67.3 , 288.7 ± 44.9 , 282.2 ± 88.8 , and 190.2 ± 56.8 , in patients with creatinine clearances of ≥ 90 , 60 to 89, 30 to 59, and < 30 ml/min ($P < 0.001$). Mean daily doses $\pm$ SD (mg) of PMB (gray diamond) were 162.5 ± 40.3 , 160.6 ± 35.8 , 153.9 ± 41.8 , and 145.0 ± 32.1 in patients with creatinine clearances of ≥ 90 , 60 to 89, 30 to 59, < 30 ml/min ($P < 0.012$).

eight (71.6%) patients in the CMS group received a mean daily dose of 300 mg of CBA (equivalent to 9,000,000 IU of CMS), and 11 (19.0%) of them received CBA doses between 300 and 450 mg. In the PMB group, 296 (72.2%) patients received a mean daily dose of ≥ 150 mg/day (a dose associated with increased risk for RF in this population) (12). Of these, 99 (33.5%) received doses of ≥ 200 mg/day. Twenty-two patients (27.2%) in the CMS group received a loading dose (median loading dose of 400 mg of CBA; IQR, 300 to 450) compared to no patients in the PMB group. Median treatment duration was 13 days (IQR, 10 to 15) for CMS and 10 days (IQR, 7 to 14) for PMB ($P < 0.001$).

The overall incidence of RF was 16.9% (83 of 491) during polymyxin therapy, and it was significantly higher in CMS-treated patients (38.3%) than in PMB-treated patients (12.7%) (relative risk, 4.27; 95% confidence interval [CI], 2.5 to 7.3; $P < 0.001$). The median time from polymyxin initiation to RF was 7 days (IQR, 3 to 12); 7 days (IQR, 7 to 11) and 7 days (IQR, 3 to 12) ($P = 0.48$) in CMS and PMB groups, respectively. The incidence of RF was higher in the CMS group regardless of baseline creatinine clearance strata (Fig. 1). A summary of the main results and the results of subgroup analyses are shown in Table 2. Bivariate analysis of risk factors for RF is shown in Table 3.

In multivariate analysis, CMS therapy was an independent risk factor for RF along with ICU admission, higher weight, older age,

and bloodstream and intraabdominal infection (Table 4). The results were not modified with the inclusion of Charlson score, use of vasoactive drugs, or baseline creatinine clearance when forced into the model to adjust for residual confounding (Table 4). Sensitivity analysis with exclusion of one participating center at a time showed that CMS remained as an independent risk factor for RF in all models (see Table S1 in the supplemental material). Since we only considered the use of vasoactive drugs in patients who initiated these drugs on the first day of polymyxin therapy (as a marker of severity of illness), we also performed a sensitivity analysis considering the worst-case scenario, in which all CMS patients who developed renal failure would have received vasoactive agents. The main results were not changed by either adding vasoactive drugs into the Cox regression model or replacing ICU admission with vasoactive drugs in the model (see Table S2 in the supplemental material). Multivariate analyses of subgroups are shown in Table 5.

Among the patients treated with CMS, those who received loading doses presented higher rates of RF (17 of 22, 77.3%) than those who did not receive loading doses (14 of 59, 23.7%) ($P \leq 0.001$). A *post hoc* analysis revealed that patients who received a loading dose had significantly lower creatinine clearance than those who did not receive a loading dose (61.0 ± 41.7 versus 105.0 ± 65.8 ml/min, respectively; $P = 0.001$); they also tended to

TABLE 2 Overall incidence of acute kidney injury, incidence of renal failure, and incidence in subgroups

Incident	Total no. (%), <i>n</i> = 491	No. for CMS (%), <i>n</i> = 81	No. for PMB (%), <i>n</i> = 410	<i>P</i> value
Incidence of renal failure	83 (16.9)	31 (38.3)	52 (12.7)	<0.001
Any degree of AKI	249 (50.7)	60 (74.1)	189 (46.1)	<0.001
Other RIFLE classes				<0.001 ^a
Risk	112 (22.8)	20 (24.7)	92 (22.4)	
Injury	54 (11.0)	9 (15.0)	45 (11.0)	
ICU patients	281 (57.2)	59 (72.8%)	222 (54.1)	
Renal failure	62 (22.1)	27 (45.8)	35 (15.8)	<0.001
Non-ICU patients	210 (42.8)	22 (27.2)	199 (45.9)	
Renal failure	21 (10.0)	4 (18.2)	19 (9.0)	0.25
Baseline creatinine clearance of ≥60 ml/min	245 (49.9)	53 (65.4)	192 (46.8)	
Renal failure	44 (18.0)	19 (35.8)	25 (13.0)	<0.001
Baseline creatinine clearance of <60 ml/min	246 (50.1)	28 (34.6)	218 (53.3)	
Renal failure	39 (15.9)	12 (42.9)	27 (12.4)	0.01
High dose of polymyxins ^b	353 (71.9)	58 (71.6)	295 (71.9)	
Renal failure	71 (20.1)	21 (36.2)	50 (16.9)	0.002

^a Considering a 4 by 2 cross table with the categories “no AKI, risk, injury, and failure.”

^b High doses of CMS were ≥300 mg/day, and high doses of PMB were ≥150 mg/day.

be older (mean age, 58.5 ± 16.4 versus 49.9 ± 17.9 years; *P* = 0.052) and to have a higher median Charlson score (2 with an IQR of 1 to 3 versus 1 with an IQR of 0 to 2; *P* = 0.09). None of the eight patients who presented bloodstream infections received loading doses. The two groups received similar mean total daily doses (*P* = 0.37) and similar doses in milligrams per kilogram (*P* = 0.74) and presented similar characteristics regarding the other associated variables evaluated in the multivariate model, including weight (*P* = 0.73), intraabdominal infections (*P* = 0.81), use of vasoactive drugs (*P* = 0.51), and ICU admission (*P* = 0.27). When adjusted for age (*P* = 0.05), baseline creatinine clearance (*P* = 0.06), and Charlson score (*P* = 0.76) in a Cox regression model, loading doses were significantly associated with RF (adjusted hazard ratio [HR], 5.2; 95% CI, 2.3 to 12.0; *P* ≤ 0.001). The addition of ICU admission (*P* = 0.48) to the regression model did not affect the results regarding loading dose (adjusted HR, 5.0; 95% CI, 2.17 to 11.5; *P* ≤ 0.001).

The overall 30-day mortality was 40.1% (197 of 491) with 30.9% (25 patients) and 43.4% (178 patients) in the CMS and PMB groups, respectively (*P* = 0.083). Patients who developed RF presented higher 30-day mortality rates (50.6%, 42/83 patients) than those who did not develop RF (38.0%, 155/408 patients) (*P* = 0.044). A multivariate model revealed no difference in mortality among patients receiving CMS versus those receiving PMB (HR, 0.89; 95% CI, 0.56 to 1.38; *P* = 0.57) after adjustment for age (*P* < 0.001), ICU admission (*P* < 0.001), and Charlson comorbidity score (*P* < 0.001). RF (HR, 1.28; 95% CI, 0.90 to 1.81; *P* = 0.17) was also not independently associated with 30-day mortality when adjusted for age (*P* < 0.001), ICU admission (*P* < 0.001), and Charlson score (*P* < 0.001).

DISCUSSION

In our study, patients treated with CMS presented significantly higher rates of RF than those treated with PMB. The observed increase in risk persisted after adjustment for other important

covariates associated with RF, such as weight, age, ICU admission, and site of infection.

It is unlikely that baseline comorbidities and severity of illness affected the results, as evidenced by forcing Charlson index and use of vasoactive drugs into the multivariate model. Furthermore, a higher incidence of RF was also observed with CMS in the subgroup of ICU patients after adjustment for APACHE II score, corroborating the notion that severity of illness did not explain our results. The incidence of RF was also lower in non-ICU patients treated with PMB; however, this comparison did not reach statistical significance, probably because of the low number of patients but especially because of the low number of the events (RF).

The results were also unchanged by forcing baseline creatinine clearance into the model. Additionally, patients treated with CMS presented higher RF rates in distinct categories of baseline creatinine clearance despite the similar mean doses of PMB among all categories. CMS remained an independent risk factor for RF in the multivariate analysis of baseline creatinine clearance at ≥60 ml/min and <60 ml/min. Ultimately, these findings indicate that the risk of RF associated with CMS treatment is increased regardless of renal function.

Our findings corroborate those of recent studies reporting higher AKI rates in patients treated with CMS compared to those treated with PMB (5, 9). Nonetheless, the main outcome of these studies was any degree of AKI as defined by RIFLE. Even if other covariates are adequately controlled, the use of any degree of AKI as the main outcome may be subject to residual confounding. We chose to evaluate RF as the primary outcome because it is less susceptible to smaller variations in creatinine values that can be caused by many other determinants (15). We also chose to analyze data using a Cox proportional hazards model because it takes into account the time elapsed between the beginning of exposure and the actual event, which varies in distinct patients, as occurred in our study.

TABLE 3 Potential risk factors for renal failure according to RIFLE score

Variable ^a	Renal failure		P value
	Yes (n = 83)	No (n = 408)	
Gender, male	56 (67.5)	240 (58.8)	0.18
Age, yr	62.8 ± 13.7	61.9.0 ± 18.3	0.634
Weight, kg	72.5 ± 15.2	65.8 ± 15.7	<0.001
Body mass index	25.6 ± 5.3	23.9 ± 5.4	0.009
Baseline creatinine clearance, ml/min	73.3 ± 57.1	72.9 ± 50.0	0.951
Infection site			
Respiratory tract	46 (55.4)	260 (63.7)	0.194
Bacteremia	14 (16.9)	40 (9.8)	0.092
Urinary tract	11 (13.3)	38 (9.3)	0.373
Abdominal	12 (14.5)	21 (5.1)	0.004
Other	7 (8.4)	71 (17.4)	0.061
Other nephrotoxic drug	63 (75.9)	299 (73.3)	0.721
Aminoglycoside	9 (10.8)	39 (9.6)	0.876
Vancomycin	44 (53.0)	202 (49.5)	0.645
NSAID	0	3 (0.7)	0.99
Furosemide	23 (27.7)	141 (34.6)	0.281
Amphotericin B	2 (2.4)	5 (1.2)	0.337
Acyclovir/ganciclovir	5 (6.0)	28 (6.9)	0.970
Nephrotoxic contrast	8 (9.6)	44 (10.8)	0.910
Microbiologically confirmed infection	60 (72.3)	241 (59.1)	0.033
Vasoactive drug	32 (38.6)	100 (24.5)	0.013
ICU admission	62 (74.7)	219 (53.7)	<0.001
Cardiovascular disease	44 (53.0)	211 (51.7)	0.924
Diabetes	15 (18.1)	86 (21.1)	0.639
Charlson	2 (1–3)	2 (1–4)	0.009
CMS ^b	31 (37.3)	50 (12.3)	<0.001

^a Data are presented as number (%), mean ± SD, or median (interquartile range).^b Twenty-two patients received loading doses of CMS; 17 (77.3%) presented renal failure compared with 14 (23.3%) of 59 patients who did not receive a loading dose ($P < 0.001$).

Two previous studies did not detect statistically significant differences in AKI rates with CMS or PMB (10, 13), even though crude AKI incidence was higher in CMS in the study by Tuon et al. (10). Oliveira et al. did not observe any differences in nephrotox-

icity rates (13). Nonetheless, the definition of nephrotoxicity in that study was not based on standardized criteria, such as RIFLE for example, and the incidence of AKI may have been underestimated.

Additionally, in contrast with most previous studies (5, 9, 13), we analyzed patients treated according to the most recent pharmacokinetic recommendations, including loading doses for CMS (17) and no adjustment of PMB doses according to creatinine clearance (18). It is possible that in previous studies the low doses of PMB administered to patients with decreased creatinine clearance may, at least in part, explain the lower rates of AKI found in PMB groups. Even though there was a significant decrease in the daily dose given to patients treated with PMB in the presence of creatinine clearance of <30 ml/min (Fig. 1 legend) in our study, the absolute value was very similar to that given to patients with creatinine clearances of >30 ml/min, and the rates of RF remained lower. Although CMS and PMB doses cannot be directly compared, decreasing the doses of either of these agents may lead to decreased incidence of AKI since higher doses of the two polymyxins have been found to be a major risk factor for nephrotoxicity (9, 12). Thus, we compared the incidences of RF in patients receiving “high” daily doses of polymyxins (≥ 300 mg of CBA and ≥ 150 mg of PMB), associated with a significantly higher risk of RF (12, 14), and the results pointed toward the same direction. The analysis, including only patients receiving ≥ 200 mg of PMB, yielded similar results. These analyses minimized a potential effect of the doses of each individual polymyxin on the outcome and corroborate the major finding of our study.

Although it was not a goal of our study, we found that loading doses were significantly associated with higher rates of RF in CMS-treated patients, a fact that was not observed in a previous evaluation (22). However, this finding requires further evaluation with a higher number of patients receiving loading doses. Also, it does not fully explain the higher rates of RF observed in CMS-treated patients because the results were not different when patients receiving loading doses were excluded from the analysis (adjusted HR, 1.96; 95% CI, 1.0 to 4.4; $P = 0.05$; data not shown), though it must be acknowledged that the effect size has reduced with these exclusions. Finally, it must be underscored that CMS loading doses are mandatory to achieve faster and adequate conversion of CMS into colistin in the beginning of therapy (23, 24).

Regardless of dose issues, we raised two hypotheses to explain the increased rates of nephrotoxicity with CMS since both colistin and PMB have been shown to present similar *in vitro* toxicity to

TABLE 4 Cox proportional hazards regression models for renal failure^b

Variable	Final model ^a		Alternative model 1		Alternative model 2		Alternative model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
CMS	3.35 (2.05–5.48)	<0.001	3.36 (2.02–5.06)	<0.001	3.30 (2.02–5.39)	<0.001	3.36 (2.06–5.48)	<0.001
ICU	1.98 (1.19–3.29)	0.008	1.98 (1.19–3.31)	0.009	1.86 (1.09–3.19)	0.024	1.97 (1.19–3.28)	0.009
Weight (kg)	1.02 (1.01–1.03)	0.001	1.02 (1.01–1.03)	0.001	1.02 (1.01–1.03)	0.02	1.02 (1.01–1.04)	0.001
Age (yr)	1.02 (1.01–1.03)	0.014	1.02 (1.00–1.03)	0.014	1.02 (1.00–1.03)	0.019	1.02 (1.00–1.03)	0.052
Abdominal infection	2.43 (1.29–4.57)	0.006	2.43 (1.29–4.57)	0.006	2.38 (1.26–4.49)	0.008	2.42 (1.28–4.55)	0.006
Bacteremia	1.67 (0.93–2.99)	0.085	1.67 (0.93–3.00)	0.088	1.68 (0.94–3.00)	0.083	1.65 (0.92–2.96)	0.092
Charlson score			1.00 (0.90–1.12)	0.972				
Vasoactive drug					1.18 (0.73–1.91)	0.489		
Baseline creatinine clearance							1.00 (0.99–1.00)	0.574

^a Omnibus tests of model coefficients: $-2\log$ likelihood = 905.556; $\chi^2 = 23.510$; $P < 0.001$.^b Blank cells, not performed.

TABLE 5 Cox proportional hazards regression models for renal failure in subgroups^b

Variable	ICU, <i>n</i> = 281; CMS = 59/PMB = 222		Non-ICU, <i>n</i> = 210; CMS = 22/PMB = 188		GFR of ≥60 ml/min, <i>n</i> = 245; CMS = 53/PMB = 192		GFR of <60 ml/min, <i>n</i> = 246; CMS = 28/PMB = 218		High doses of polymyxin ^a , <i>n</i> = 353; CMS = 58/PMB = 295	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
CMS	4.27 (2.36–7.74)	<0.001	2.79 (0.89–8.81)	0.08	3.95 (1.98–7.89)	<0.001	2.53 (1.15–5.57)	0.02	2.57 (1.48–4.48)	0.001
ICU					1.41 (0.69–2.85)	0.34	2.89 (1.31–6.36)	0.01	1.73 (1.00–3.01)	0.051
Weight (kg)	1.03 (1.02–1.05)	<0.001	1.01 (0.98–1.05)	0.50	1.01 (0.99–1.03)	0.26	1.04 (1.02–1.06)	<0.001	1.02 (1.01–1.04)	0.003
Age (yr)	1.02 (1.00–1.03)	0.042	1.02 (0.99–1.04)	0.21	1.03 (1.02–1.05)	<0.001	0.98 (0.96–1.01)	0.19	1.02 (1.00–1.04)	0.01
Abdominal infection	2.84 (1.29–6.26)	0.01	2.96 (0.99–8.90)	0.53	4.12 (1.71–9.95)	0.01	1.02 (0.37–2.80)	0.98	2.63 (1.39–4.95)	0.003
Bacteremia	1.04 (0.49–2.23)	0.91	4.08 (1.52–10.9)	0.01	1.45 (0.60–3.48)	0.41	2.22 (0.97–5.08)	0.06	1.97 (1.02–3.79)	0.04
APACHE II	1.03 (0.96–1.05)	0.88								

^a High doses: CMS, ≥300 mg/day; PMB, ≥150 mg/day. Including only PMB patients who received doses ≥200 mg/day, CMS remained a significant risk factor for renal failure (HR, 2.28; 95% CI, 1.13 to 4.59; *P* = 0.021).

^b Blank cells, not performed or not applicable.

renal cells (9). First, it is possible that, even if it is minimal compared to colistin, CMS may contribute to additional injury to renal cells. Another explanation is related to the pharmacokinetic/toxicodynamic profile of CMS and colistin; increased toxicity may be related to the flatter plasma concentration curves of colistin, determined by the slow conversion of CMS into colistin (17, 25), compared to PMB concentration spikes after a 1-h infusion (18). In rats, PMB uptake by proximal tubular renal cells is saturable, i.e., high concentrations exceed the capacity of PMB reabsorption by these cells, and there is no increase in drug accumulation in the kidney (26). More fractionated administration of the same dose resulted in repeated exposure of the renal cells to nonsaturable drug concentrations and consequently caused more drug uptake by the cells. That, in turn, resulted in higher concentrations of the drug in rat kidneys, ultimately leading to a larger extent of kidney damage (26). In other words, higher peaks do not increase drug accumulation in the kidney, whereas continuously stable lower polymyxin concentrations, which occur with colistin regardless of CMS dosing interval, lead to continual uptake and higher drug accumulation in renal parenchyma (26). Although these two hypotheses are plausible, they require further investigation.

An interesting finding was that despite the increase in RF in the CMS group, 30-day mortality was not different in CMS- and PMB-treated patients in adjusted analyses. Nevertheless, RF was not independently associated with mortality in our study when adjusted for other covariates, and this may explain the overall similar mortality in the two groups. However, it is important to emphasize that our study was not designed to compare mortality between polymyxin groups. Important variables, such as microbiological susceptibility, combination therapy with another active antimicrobial, and time to appropriate antibiotic treatment, were not evaluated. These limitations preclude definitive conclusions regarding mortality. Therefore, the relation among polymyxins, development of RF, and death should be further investigated.

Our study was limited because CMS-treated patients were not from the same centers as those receiving PMB. Differences in patient characteristics and the care provided at each center may have contributed to the differences found in RF rates. For this reason, we performed a sensitivity analysis, excluding one center at a time in the multivariate model to account for center bias. The results remained consistent, showing significantly higher rates of RF with CMS in all models. We also only considered the use of vasoactive drugs initiated on the first day of polymyxin therapy as a marker of

disease severity, but we did not account for the potential nephrotoxic effect of vasoactive drugs if initiated after the first day of polymyxin therapy. However, our sensitivity analysis considering the “worst-case scenario,” favoring the CMS group, showed that the main finding of higher incidence of RF with CMS was not affected. Finally, although there was a strict evaluation of other clinically important variables in multivariate models, we cannot rule out a residual confounding effect on our results.

In summary, our study showed that CMS-treated patients presented higher rates of RF than PMB-treated patients. Our findings suggest that CMS may be more nephrotoxic than PMB. Further studies are necessary to confirm the observed differences in nephrotoxicity and effect size in other patient populations.

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