Incidence of Nephrotoxicity Associated with Intravenous Colistimethate Sodium Administration for the Treatment of Multidrug-resistant Gram-negative Bacterial Infections

Svetlana Sadyrbaeva-Dolgova (sadyrbaeva@gmail.com)
Hospital Universitario Virgen de las Nieves
Ricardo García-Fumero
Hospital Universitario Virgen de las Nieves
Alberto Jimenez-Morales
Hospital Universitario Virgen de las Nieves
Juan Pasquau
Hospital Universitario Virgen de las Nieves
Carmen Hidalgo-Tenorio
Hospital Universitario Virgen de las Nieves

Research Article

Keywords:

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1246386/v1

Abstract

Colistimethate sodium (CMS) is the inactive prodrug of colistin, CMS has a narrow antibacterial spectrum with concentration-dependent bactericidal activity against multidrug-resistant gram-negative bacteria, including *P. aeruginosa* and *Acinetobacter baumannii.* This study aimed to analyze potential correlations between clinical features and the development of CMS-induced nephrotoxicity. This retrospective cohort study was conducted in a tertiary-care university hospital between 1 January 2015 and 31 December 2019. A total of 163 patients received CMS therapy. 75 patients (46%) developed nephrotoxicity attributable to colistin treatment, although only 14 patients (8.6%) discontinued treatment for this reason. 95.7% of CMS were prescribed as target therapy. *Acinetobacter baumanii* spp. was the most commonly identified pathogen (72.4%) followed by *Pseudomonas aeruginosa* (19.6%). Several risk factors associated with nephrotoxicity were identified, among these were Charlson Index (OR 1.29, 95%CI 1.02–1.62; p = 0.032); admission to the ICU (OR 4.25, 95%CI 1.63–11.07, p = 0.003) and cumulative dose per patient (OR 1.03, 95% CI 1.01–1.05, p = 0.003). In terms of in-hospital mortality, risk factors were male sex (OR 2.43, 95%CI 1.06–5.56, p = 0.035); age (OR 1.03, 95%CI 1.01–1.05, p = 0.043) and higher maintenance doses (OR 1.21, 95%CI 1.03–1.43, p = 0.023). Nephrotoxicity due to CMS treatment was not related to mortality (OR 1.42, 95%CI 0.68–2.99, p = 0.351). In conclusion, it was shown once again that CMS is a drug with a high incidence of nephrotoxicity. Its complex management, administering the loading dose and monitoring creatinine at least every 48 hours, with consequent adjustment of the maintenance dosage, leads to a high percentage of inappropriate use.

Introduction

Severe nosocomial infections due to multidrug-resistant gram-negative bacteria (MDR-GNB) are deemed to be of high morbidity and mortality. The emergence of highly resistant gram-negative bacteria, in particular carbapenem-resistant *Acinetobacter baumanii* (CRAB) strains, multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella* species, and the lack of effective antimicrobials, have led to reuse polymyxins, antibiotics available since 1950 but abandoned owing to their nephrotoxicity.

Colistin E is a polypeptide belonging to the polymyxin family, produced by *Bacillus polymyxa* subspecies *colistinus*[1]. Colistin's structure includes a polycationic peptide ring composed of 10 amino acids and a hydrophobic fatty acid tail[2]. It consists of at least 30 components, the 2 major ones being colistin A and colistin B[3].

Colistimethate sodium (CMS) is the inactive prodrug of colistin, a polymyxin that can be administered parenterally or by inhalation. CMS undergoes a rapid hydrolysis to methanesulfonated derivatives and to colistin. It is shown that colistin concentrations increase slowly after CMS administration in critically ill patients and it takes 2 days to reach steady state, suggesting the benefits of initiating treatment with a loading dose.[4,5]

CMS has a narrow antibacterial spectrum with concentration-dependent bactericidal activity against MDR-GNB, including *P. aeruginosa* and *Acinetobacter baumannii*. The mechanism of action of CMS involves interaction between the polycationic portion and the anionic portion of lipopolysaccharides (LPS) that compound the outer membrane, disrupting the outer membrane of gram-negative bacteria and providing bactericidal activity and probable enhancement of the activity of other antimicrobials [6]. Numerous antibiotics have shown synergistic activity with colistin in vitro; the most studied are rifampicin and imipenem, but also ceftazidime[7,8].

The most common adverse reaction of CMS is nephrotoxicity and neurotoxicity. Nephrotoxicity usually occurs within a median of 2.5 to 10 days of therapy [9–11] and renal function usually returns to normal within 3 to 9 weeks after treatment discontinuation[12]. Colistin induces tubular damage by increasing the membrane permeability of epithelial cells, which increases influx of cations, anions and water, leading to leakage of contents and cell death. The proposed mechanism is related to its mechanism of action against gram-negative bacteria[9] and has shown a dose-dependent effect [11,13]. Given that nephrotoxicity is a well-known predictor of mortality [14], it has been a common measurement during CMS therapy. However, the incidence of renal function alterations in this context is not well-established yet as many unexplored risk factors might be involved. It is clear that an urgent strategy to properly use CMS therapy against MDR-GNB is needed, as the incidence of colistin-resistant gram-negative bacteria, especially *Acinetobacter spp.*, is increasing [15]. However, CMS therapy may still be an option for treating colistin-resistant CRAB infections [16], increasing interest in studying the use of this valuable antimicrobial in daily practice.

Unfortunately, it is difficult to implement a patient-based approach to select the most appropriate antimicrobial therapy against these microorganisms. Interpatient variability is extensive even at a given creatinine clearance [13], but minimizing it is crucial to enhance survival by reducing CMS-associated nephrotoxicity. This study aimed to analyze potential correlations between clinical features and the development of CMS-induced nephrotoxicity. Results may provide a more thorough understanding of that interpatient variability to avoid CMS misuse.

Materials And Methods

This retrospective cohort study was conducted in an 800-bed tertiary university hospital in Spain between 1 January 2015 and 31 December 2019.

All patients enrolled in this study (≥ 18 y.o.) have received intravenous CMS for at least 48 hours.Clinical data were gathered using the hospital electronic medical records, which contain demographic, microbiological and prescription information. Demographic and clinical characteristics of patients, including age, sex, and baseline Charlson Comorbidity Index score were included. In relation to antibiotic treatment, data were gathered related to colistin loading dose and duration, concomitant use of antibiotic, infection sites and organisms with susceptibility. Also, baseline, peak creatinine and glomerular filtration

(CKD-EPI) during colistin therapy, albumin, hemoglobin and leukocytes were collected. Only one treatment per patient and parenteral administration of the treatment were considered in the analysis; CMS administered by inhalation were excluded from the analysis.

Available colistin in our hospital is labelled GES® and is equivalent 1.000.000 UI (1 MU) of CMS is equal to 80 mg of CMS or 34 mg of colistin base activity (CBA). Therefore, the dose of 9 MU is equal to 300 mg and of 4.5MU is equal to 150 mg of CBA.

The main outcome variables were: all-cause in-hospital mortality rate, efficacy based on clinical and microbiological response to the treatment, and length of current hospital stays. Clinical success was defined as the resolution of symptoms and signs of infection; microbiological cure as the eradication of MDR-GNB isolates on follow-up cultures, and failure as the persistence or worsening of symptoms and "escalating" therapy with additional antimicrobial agents for this infection.

Nephrotoxicity was stablished following the Kidney Disease Improving Global Outcomes (KDIGO) classification, creatinine elevation of ≥ 0.3 mg/dL in 48 hours or ≥ 1.5 times baseline creatinine in an interval of up to 7 days[17].

Appropriate CMS prescription was determined as administration of a loading dose of 9 million units (MU) followed by a maintenance dose of 4.5 MU administered every 12 hours or 3 MU every 8 hours. In patients with moderate to severe renal impairment after a loading dose of 9 MU, maintenance doses were adjusted according to CKD-EPI clearance estimates.

Combination therapy was considered when both antimicrobials were active against gram-negative microorganisms.

This study was approved by the local ethics committees (Comité de Ética de la Investigación (CEI/CEIM) de la Provincia de Granada) and the requirement for informed consent was waived for performing this study. Data collection was complied with the Helsinki declaration principles and biomedical research legislation (Law 3/2018, December 5).

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Statistical analysis:

Means, standard deviations, medians, and interquartile range were calculated for quantitative variables, and absolute and relative frequencies for qualitative variables. Relations among qualitative variables were analyzed using Pearson's or Fisher's chi-square test, while quantitative variables with non-normal distribution (Kolmogorov-Smirnov test) were analyzed with the non-parametric Mann-Whitney test.

A multivariate logistic regression model was constructed using backward stepwise selection considering entry criteria of $p \leq 0.05$ and exit criteria of $p > 0.25$. All variables that showed statistical significance in

bivariate analysis or were otherwise considered relevant were included. Results with p≤ 0.05 were considered statistically significant. Data management and analysis were performed using IBM SPSS Statistics 19 software.

Results

1. Descriptive analysis of the cohort

The study included 163 patients with CMS prescriptions over 5 years. The mean age was 66 years, and 71.2% were male.

At the time of CMS initiation, almost half of the patients were admitted to the Intensive Care Unit ICU (42.3%). The median basal glomerular filtration rate estimated according to CKD-EPI was 92.2 ml/min/1.73m2. The most frequent infection where CMS was prescribed was lower respiratory tract infection (41.7%) followed by urinary tract infection (22.7%) and others. 17.2% of all infections were associated with bacteremia.

Other characteristics of the patients are shown in Table1.

Regarding CMS prescriptions, 95.7% were prescribed as target therapy. Most of them given in combination therapy (64.4%) with one or two antimicrobials against gram-negative pathogens, 51.5% and 12.9% respectively. The antibiotics mainly used in combination therapy were carbapenems (34.0%) and tigecycline (24.0%). Thirty-five patients (24.5%) received a loading dose. The CMS prescriptions adjusted following variation of serum creatinine were 28.2%. Hence, CMS prescriptions were appropriate for 25 patients (15.3%). The median duration of CMS treatment was 10 days (IQR: 6-14) and the median cumulative dose per patient was 63MU (IQR: 36-108).

Acinetobacter baumanii spp. was the most commonly identified pathogen (72.4%) followed by *Pseudomonas aeruginosa* (19.6%), *Klebsiella* spp. (4.3%) and *Enterobacter* spp. (1.8%), (Table 1). Only 4.3% of patients were treated empirically with CMS.

75 patients (46%) developed nephrotoxicity attributable to colistin treatment, although only 14 patients (8.6%) discontinued treatment for this reason. The median onset time of nephrotoxicity after initiation of CMS treatment was 7 days (IQR: 4-11).

Therefore, the reasons for discontinuation of CMS treatment were cure (57.7%) followed by patient's death (17.8%), and treatment adjustment by isolated microorganism (10.4%), among others (Table1).

2. Risk factor associated with nephrotoxicity

In the bivariate analysis of factors associated with the incidence of nephrotoxicity, the following were found: age (70.4 years vs 62.2 years, p=0.003), Charlson Index (2 vs 1.5, p=0.012), Basal Glomerular Filtration Rate (82.7 ml/min/1.73m vs 105.7 ml/min/1.73m, p<0.001) and hemoglobin levels (9.5 vs 10.3,

p< 0.001). Patients were also stratified according to baseline clearance, and those with baseline clearance below 75 ml/min/1.73m had a higher incidence rate of nephrotoxicity (68%, p=0.041) (Table 2). Furthermore, in this group of patients, the source of infection was other than respiratory (70.7%vs 47.7%, p=0.003). The duration of treatment with CMS was longer (12 days vs 9 days, p=0.009) and consequently the cumulative dose was higher (78 MU vs 60 MU, p=0.013). Due to nephrotoxicity, a higher percentage of dose adjustment was performed in these patients (37.3% vs 20.5%, p=0.017). In addition, in patients with nephrotoxicity, the rate of appropriate prescription was lower (9.3% vs 20.5%, p=0.050) Table1.

Regarding clinical outcomes, the higher mortality rate corresponded to patients with nephrotoxicity (44.0% vs 27.3%, p=0.027), lowest cure rate (48.0% vs 65.9%p=0.022), and shorter hospital stay (45 days vs 52 days; p=0.049). Table 3.

In the multivariate analysis, the risk factors that independently were associated with nephrotoxicity were Charlson Index (OR 1.29, 95%CI 1.02-1.62; p=0.032); admission to the ICU (OR 4.25, 95%CI 1.63-11.07, p=0.003) and cumulative dose per patient (OR 1.03, 95% CI 1.01-1.05, p=0.003). However, high creatinine clarence (OR 0.95, 95%CI 0.93-0.97), respiratory infection (OR 0.16, 95%CI 0.06-0.39) and appropriate CMS prescription (OR 0.29, 95%CI 0.08-1.03, p=0.056) were found to be protective factors against the onset of nephrotoxicity. Table 4.

3. Risk factor associated with in-hospital mortality

To assess the impact of nephrotoxicity on mortality, a univariate analysis was carried out. Risk factors associated with mortality were identified, including: age (OR 1.02, 95%CI 1.0-1.05, p=0.048) and nephrotoxicity (OR 2.09, 95%CI 1.09-4.03, p=0.027); on the other hand, serum hemoglobin proved to be a protective factor (OR 0.83, 95%CI 0.69-0.99, p=0.038).

Furthermore, mortality rate was compared according to the onset of nephrotoxicity at 7 days or later and statistically significant difference was found (OR 2.95, 95%CI 1.14-7.63; p=0.024). Patients who developed nephrotoxicity within the first 7 days after initiation of treatment have a higher mortality rate (57.5% vs 31.4%) (Table 6).

However, in the multivariate analysis risk factors associated with mortality were male sex (OR 2.43, 95%CI 1.06-5.56, p=0.035); age (OR 1.03, 95%CI 1.01-1.05, p=0.043) and higher maintenance doses (OR 1.21, 95%CI 1.03-1.43, p=0.023). Nephrotoxicity due to CMS treatment was not related to mortality (OR 1.42, 95%CI 0.68-2.99, p=0.351).

Otherwise, serum hemoglobin levels and length of hospital stay were protective factors against mortality (OR 0.76, 95%CI 0.63-0.92, p=0.005 and OR 0.99, 95%CI 0.98-1.00, p=0.046 respectively) Table 5.

Discussion

CMS is a drug that was rarely used until recently, but with the emerging rise of multidrug-resistant microorganisms as carbapenemase-producing Enterobacteriaceae and the lack of therapeutic arsenal, it

has been reintroduced into clinical practice.

This study shows impact of dosage and duration on the incidence of nephrotoxicity. Nephrotoxicity due to treatment developed in almost half of the patients, taking into account that only in one third of them the dosage was adjusted according to variations in renal clearance rates and that the loading dose was used in only one quarter. These results may suggest that the issue is not colistin itself but its inappropriate use

Patients who did not develop nephrotoxicity during treatment had a higher percentage of appropriate CMS prescriptions (20.5% vs. 9.3%, p = 0.05). On the other hand, longer treatments with CMS obviously increased the incidence of renal function alteration (9 days vs 12 days, p = 0.009). This may be due to CMS delay in reaching steady state for about 48 hours without the loading dosage which may, therefore, delay the onset of clinical efficacy of the drug, increasing treatment duration and worsening the clinical outcomes of the patients[9].

In a retrospective study including 115 patients treated with CMS, nephrotoxicity appeared in 14% of them. The dosage of CMS was adjusted to each patient's renal clearance and all patients undergoing continuous renal replacement therapy were excluded [18]. Nevertheless, therapeutic success was achieved in half of them, similar to the results obtained in our study. Although, in other studies, clinical cure data were comparatively higher – 82.1%- which could be due to the reduced number of patients analyzed, only 28.1%[9].

Multidrug-resistant *A. baumannii* was the most frequent microorganism treated with CMS and, in more than half of the cases, CMS was administered in combination therapy -mostly with carbapenems and tigecycline- with poor results. This fact supports the idea of the need of increasing research for new antibiotics, in addition to faster approval by the evaluating agencies of drugs that already exist and are more effective, less toxic and easier to use than CMS, such as Cefiderocol or Aztreonam/avibactam.

Moreover, in the empirical treatment of infections caused by multidrug-resistant bacteria in critically ill or severe patients we believe that combination therapy should be the strategy to be employed [19]. In contrast to this opinion, there are some studies such as the one carried out in patients with infections caused by *A. baumanii* in which CMS was compared in monotherapy and in combination therapy with tigecycline at standard dosage [20]. These studies found that patients receiving the association of Tigecycline with a high dosage of CMS did not present the expected decrease in crude mortality. It should be considered that in this study only bacteremias were analyzed, mostly with respiratory foci and with a dosage of tigecycline of 50mg/12h. For these indications, it is known that tigecycline does not improve clinical outcomes [21]. This may be due to two reasons: firstly, the dosage of Tigecycline used in respiratory infections has shown to be insufficient and led to a higher failure rate in a clinical trial in which it was compared to Imipenem-cilastatin[22]; secondly, given its pharmacokinetics and pharmacodynamics, it is not recommended for use in bacteremia [23]. In our study, there were only 17% of bacteremias and most of

the patients with respiratory infections treated with tigecycline received high dosage - a 200 mg loading dose followed by 100 mg/12h.

Another study, in which clinical outcomes were analyzed after treatment of *A. baumanii* infections, showed better results in the group treated with CMS monotherapy than in combination with meropenem[16]. In this study, the mortality rate was lower with CMS-resistant isolates due to loss of virulence compared to CMS-sensitive strains. We did not find a statistically significant relationship between combined treatment and mortality. However, patients treated with three antibiotics active against gram-negative bacteria had a higher incidence of nephrotoxicity. In addition, it should be considered the presence of heteroresistance in strains apparently sensitive to colistin, which may become resistant during treatment [24]. In order to avoid this and to ensure the effectiveness of colistin during treatment, it is crucial not to use CMS in monotherapy and at low dosages.

Hence, to avoid antibiotic pressure and selection of multi-resistant microorganisms, it is necessary to use colistin in combination therapy; however, and more importantly, in terms of clinical results, it is not clear which association is better in case of infections caused by *A.baumanii*, especially when the second antibiotic is not active[25,26].

It has been shown that nephrotoxicity is related to the accumulated dosage of CMS per patient[27], which is also the result of our study. This could be explained by the chemical structure of the drug and its mechanism of action. Despite the high incidence of serum creatinine alteration (46%), treatment was interrupted in only 8.6% of the patients. However, in another retrospective study with a cohort of patients similar to ours, the incidence of nephrotoxicity was 60.4% (95% CI, 50.8%-69.2%)[28]. Furthermore, it was previously found that low hematocrit levels have been associated with nephrotoxicity, although it is difficult to explain the relationship in critically ill patients, often with fluid overload[11].

Our study has some limitations. It has a retrospective design without a control group and was performed in only one medical center. Serum concentrations of CMS were not measured to verify the correlation between CMS serum levels and increased creatinine levels in blood. Moreover, daily creatinine monitoring in patients on CMS treatment is not common.

Nevertheless, we would like to underline that only a very small number of hospitals in Spain have monitoring of serum CMS levels in order to optimize pk/pd parameters and improve clinical outcomes. Monitoring CMS with creatinine levels alone is not an optimal strategy for a wide range of reasons.

In terms of strengths, this study includes a larger number of patients than those published to date, and supports the existing evidence on the use of this drug and its impact on renal function.

In conclusion, it was shown once again that CMS is a drug with a high incidence of nephrotoxicity. Its complex management, administering the loading dose and monitoring creatinine at least every 48 hours, with consequent adjustment of the maintenance dosage, leads to a high percentage of inappropriate use. Nowadays, it remains though one of the few treatment alternatives for life-threatening infections caused

by multidrug-resistant gram-negative bacilli. Therefore, we will have to continue using it despite its poor results if the procedures with new antibiotics are not facilitated and more investment is not made in the research of new molecules for these microorganisms.

Declarations

Authors contributions:

SSD: conceived and designed the study, collected the data, performed the analysis, wrote the manuscript.

RGF: collected the data, wrote the manuscript.

AJM: critical review of the manuscript

JP: critical review of the manuscript

CHT: critical review and wrote the paper.

All authors review the manuscript

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Tables

Table 1: Characteristics of patients in the study cohort

Characteristics of patients	Total(n=163)	Nephrotoxicity group n=75(46%)	Non-nephrotoxicity group n=88(54.0%)	p
Sex,male,n(%)	116(71.2)	50(66.7)	65(75.0)	0.242
Age,years,mean(SD)	65.93±15.98	70.4±12.35	62.2±17.73	**0.003**
Charlson index score,median(IQR)	2(1-3)	2(1-4)	1.5(0-3)	**0.012**
Setting: ICU vs others	69(42.3)	34(45.3)	35(39.8)	0.474
Basal Glomerular Filtration Rate(eGFR), ml/min/1.73m, median(IQR)	92.2(75-113.5)	82.7(49.5-98.2)	105.7(90.2-122.9)	**<0.001**
Creatinine basal,mg/dL, mean(SD)	0.89±0.78	1.12±0.91	0.7±0.61	<0.001
Albumin,median,mean(SD)	3.14±0.75	3.14±0.83	3.13±0.68	0.568
Hemoglobin,mean(SD)	9.91±2.01	9.45±1.51	10.31±2.30	**<0.001**
Leucocites,cells/ml*10^3, median(IQR)	10.3(7.0-15.2)	9.48(6.7-13.8)	10.9(7.3-15.6)	0.312
Protein Reactive C, median(IQR)	119.2(40.5-176.5)	122.1(52.2-194.5)	102.5(32.1-167.9)	0.134
Respiratory tract infections,n(%) Others	68(41.7) 95(58.3)	22(29.3) 53(70.7)	46(52.3) 42(47.7)	**0.003**
Bloodstream infection, n(%)	28(17.2)	12(16.0)	16(18.2)	0.713
Target therapy, n(%)	156(95.7)	71(94.7)	85(96.6)	0.546
Appropriate treatment, n(%)	25(15.3)	7 (9.3)	18(20.5)	**0.050**
Combination therapy,n(%)	105(64.4)	48(64.0)	57(64.8)	0.918
Number of associated antibiotics: -with one antimicrobial -with two antimicrobials	 84/105(51.5) 21/105(12.9)	 34(40.5) 14(29.2)	 50(59.5) 7(12.3)	 **0.031**

Antibiotics used in combined therapy:				
Types (%):				
Carbapenems				
Tigecycline	33.95			
Aminoglycosides	24.0			
Fosfomycin	11.95			
Fluroquinolones	11.4			
Other's beta-lactams	10.1			
	19.15			
Loading dose, n(%)	35(24.5)	23(30.7)	18(20.5)	0.134
Maintenance dose,median(IQR)	7.5(6-9)	9(6-9)	6(6-9)	0.499
Cumulative dose per patient, median(IQR)	63(36-108)	78(50-126)	60(36-90)	**0.013**
Dose adjustment by eGFR	46(28.2)	28(37.3)	18(20.5)	0.017
Duration of CMS therapy,median(IQR)	10(6-14)	12(7-15)	9(6-14)	**0.009**
Microorganisms, n(%)				
Acinetobacter spp.	118(72.4)	57(76.0)	61(69.3)	0.125
Pseudomonas spp.	32(19.6)	9(12.0)	23(26.1)	
Klebsiella spp.	7(4.3)	5(6.7)	2(2.3)	
Enterobacter spp.	3(1.8)	2(2.7)	1(1.1)	
Negative results	3(1.8)	2(2.7)	1(1.1	
Reasons for CMS discontinuation, n(%):				–
End of the treatment	94(57.7)	36(48.0)	58(65.9)	
Nephrotoxicity	14(8.6)	14(18.7)	0(0.0)	
Deterioration	7(4.3)	4(5.3)	3(3.4)	
Death	29(17.8)	15(20.0)	14(15.9)	
Adjustment of antibiotics	17(10.4)	6(8.0)	11(12.5)	
Allergic reaction	2(1.2)	0(0.0)	2(2.3)	

Table 2: Incidence of nephrotoxicity stratified by baseline creatinine clearance

	Baseline Glomerular Filtration Rate(eGFR), ml/min/1.73m			
	≤75	75.1-92	92.1-113.5	≥113.6
Incidence of Nephrotoxicity,n(%)	28(68.3)*	25(61.0)	15(36.6)	7(17.5)

*p=0,041

Table 3: Clinical outcomes of patients treated with CMS

Characteristics of patients	Total(n=163)	Nephrotoxicity group n=75(46%)	Non-nephrotoxicity group n=88(54.0)	OR, 95%IC	p
Duration hospital stay,days,median(IQR)	48(29-94)	45(29-76)	52(27-106)	0.99(0.98-1.00)	0.049
Clinical success, n(%)	94(57.7)	36(48.0)	58(65.9)	0.48(0.25-0.89)	0.022
In-hospital mortality, n(%)	57(35.0)	33(44.0)	24(27.3)	2.09(1.09-4.03)	0.027

Table 4: Univariable and multivariable analysis of risk factors for nephrotoxicity

Variable	**Univariable**		**Multivariable**	
	OR (95%CI)	**p**	**OR (95%CI)**	**p**
Sex,male,n(%)	0.67(0.34-1.32)	0.243		
Age,years,mean(SD)	**1.04(1.01-1.06)**	**0.002**		
Charlson index score,median(IQR)	**1.19(1.01-1.34)**	**0.033**	1.29(1.02-1.62)	0.032
Setting: ICU vs others	1.26(0.67-2.34)	0.474	4.25(1.63-11.07)	0.003
Baseline Glomerular Filtration Rate(eGFR), ml/min/1.73m, median(IQR)	**0.97(0.96-0.98)**	**<0.001**	0.95(0.93-0.97)	<0.001
Creatinine basal,mg/dL, median(IQR)	**2.9(1.39-6.02)**	**0.004**		
Albumin,median(IQR)	1.01(0.66-1.52)	0.982		
Hemoglobin,mean(SD)	**0.79(0.66-0.94)**	**0.008**		
Leucocites,cells/ml*10^3, median(IQR)	1.01(0.98-1.04)	0.422		
Protein Reactive C, median(IQR)	1.00(0.99-1.002)	0.858		
Respiratory tract infections,n(%) Others	**0.38(0.20-0.72)** Ref.	**0.003**	0.16(0.06-0.39)	<0.001
Bloodstream infection, n(%)	1.16(0.51-2.65)	0.713		
Target therapy, n(%)	0.63(0.14-2.89)	0.549		
Appropriate treatment, n(%)	**0.40(0.16-1.02**)	**0.055**	0.29(0.08-1.03)	0.056
Combination therapy,n(%)	0.97(0.51-1.84)	0.918		
2antibiotics vs gram-negative associated to CMS	2.66(1.01-6.98)	**0.048**		
Loading dose, n(%)	**1.72(0.84-3.51)**	**0.136**		

Maintenance dose,median(IQR)	1.03(0.89-1.18)	0.703		
Cumulative dose per patient,median(IQR)	**1.01(1.00-1.011)**	**0.043**	1.03(1.01-1.05)	0.003
Mantenance dose ajustment by eGFR	**2.32(1.15-4.66)**	**0.018**		
Duration of CMS therapy,median(IQR)	**1.06(1.01-1.11)**	**0.025**	0.88(0.76-1.023)	0.100
Microorganisms, n(%) *Acinetobacter* spp. Others	1.40(0.69-2.81)	0.343		

Table 5: Multivariable analysis for independent risk factors for in-hospital mortality.

	OR	95%CI	P-value
Sex,male	2.43	1.06-5.56	0.035
Age	1.03	1.01-1.05	0.043
Hemoglobin	0.76	0.63-0.92	0.005
Maintenance dose CMS	1.21	1.03-1.43	0.023
Duration hospital stay	0.99	0.98-1.00	0.046
Nephrotoxicity	1.42	0.68-2.99	0.351

Table 6: Rate of in-hospital mortality depending on the onset of nephrotoxicity

	Total(n=163)	Nephrotoxicity onset ≤ 7 days (n=40)	Nephrotoxicity onset > 7 days (n=35)	OR, 95%IC	p
In-hospital mortality, n(%)	33(44.0)	23(57.5)	11(31.4)	2.95(1.14-7.63)	0.024

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CMSnov21d1.xlsx
- supplementarymaterial.docx