



Colistin for the treatment of urinary tract infections caused by extremely drug-resistant *Pseudomonas aeruginosa*: Dose is critical



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SUMMARY

Objectives: Optimal dosage regimens of colistin for the treatment of urinary tract infections (UTI) are unknown. Colistimethate sodium (CMS), the inactive prodrug of colistin, is mainly excreted in urine and converts to colistin after filtration by glomeruli, suggesting that concentrations of colistin in urine could be much higher than in plasma. Therefore, there is a need to optimize dosage regimens of intravenous CMS for UTI. The aim of this study was to examine the relationship between AUC/MIC of formed colistin and clinical outcomes in patients with UTI caused by extremely drug resistant (XDR) *Pseudomonas aeruginosa*.

Methods: This prospective, observational cohort study involved patients with UTI caused by XDR *P. aeruginosa*. Clinical cure, bacteriological clearance and acute kidney injury (AKI) were analyzed. Steady-state colistin plasma concentrations (C_{ss}) were measured using HPLC. Based on the PK/PD of colistin in neutropenic mouse thigh infection models with *P. aeruginosa*, the optimal AUC/MIC should be ≥ 60 mg·h/L. According to the pharmacokinetics (PK) in critically-ill patients, the C_{ss} target of formed colistin in plasma was 2.5 mg/L.

Results: Thirty-three patients were included (24 lower UTI and 9 pyelonephritis). The MIC₅₀ and MIC₉₀ values for colistin were 0.5 and 2 mg/L respectively. Nineteen patients (57.6%) received colistin monotherapy (84.2% lower UTI and 15.8% pyelonephritis). Of these, clinical cure was achieved in 89.5% of cases. Among patients with clinical cure and monotherapy, only 5 (29.4%) attained an optimal plasma AUC/MIC and only 1 (5.9%) the therapeutic level of formed colistin (2.5 mg/L). However, 10 (58.8%) patients showed colistin plasma concentrations above the MIC of the isolated *P. aeruginosa*. Microbiological eradication was achieved in 76.9% of patients. AKI at the end of treatment was present in 29.4% of patients.

Conclusions: The currently recommended dosage regimens of CMS showed high efficacy for the treatment of lower complicated UTI caused by XDR *P. aeruginosa* in non-critically ill patients and in the case of low MIC values, but also a considerable nephrotoxicity rate. Our data suggest that the use of lower CMS doses for lower UTI should be investigated in future studies to minimize the unnecessary nephrotoxicity.

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Introduction

Urinary tract infection (UTI) represents between 20–49% of all nosocomial infections and *Pseudomonas aeruginosa* is the responsible of 7–10% of these cases.¹ The best therapeutic approach is controversial especially for multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* strains. Although some aminoglycosides and fosfomycin remain active against several MDR/XDR

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P. aeruginosa strains, the worrying increase in bacterial resistance coupled with the lack of new drugs in the pipeline has become a major clinical and public health concern globally.² Currently, novel agents such as ceftolozane/tazobactam and ceftazidime/avibactam have expanded the therapeutic arsenal.³ However, both in vitro and in vivo resistance have been reported with these agents.^{3–5} In this situation, until new drugs such plazomicin, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, murepavadin and cefepime-zidebactam become available in daily clinical practice,^{6–8} polymyxins represent the only therapeutic option in many cases.

Colistin is a drug with a narrow therapeutic window and nephrotoxicity is the major dose-limiting adverse effect.^{9–11} With its role as a salvage therapy for otherwise untreatable infections, it is essential to design CMS regimens that maximize its efficacy while minimizing the potential for the development of resistance and colistin-associated nephrotoxicity. The commercially available form of colistin for parenteral use is colistimethate sodium (CMS),¹² which is an inactive prodrug of colistin and 'less' toxic than colistin, the active compound. According to the package insert recommendations, current doses in Europe range from 1 to 3 million international units (IU) every 8 h in patients with normal renal function,¹³ regardless of the type of infection. Once administered, CMS converts into colistin in patients, and approximately 60–70% of the CMS dose is rapidly eliminated in the urine.^{14–16} It is believed that conversion of CMS to colistin occurs in renal tubular cells and in the bladder,^{14,17,18} suggesting that concentrations of formed colistin in the urine could be much higher than those attained in plasma. Our recent clinical PK study demonstrated that colistin urinary levels were much higher than those achieved in plasma.¹⁵ Regarding the pharmacokinetics/pharmacodynamics (PK/PD) of colistin, it is known that the index that best correlates with colistin antibacterial activity is the ratio of 24-h area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC).^{19,20} The AUC/MIC target is equal or higher than 60 mg·h/L for the treatment of infections caused by *P. aeruginosa*. Additionally, a recent population PK study suggested a target of 2.5 mg/L formed colistin in plasma at the steady state (C_{ss}).²¹ Considering the potentially very high concentration of formed colistin in urine, we hypothesized that for the treatment of UTI the plasma PK/PD target proposed for colistin is unnecessarily high and a lower dose of CMS may be sufficient to minimize the nephrotoxicity.

The main objective of this study was to examine the AUC/MIC value of formed colistin in plasma in a cohort of patients with symptomatic UTI (sUTI) caused by XDR *P. aeruginosa* and its association with clinical and microbiological outcomes. A secondary objective was to identify risk factors for colistin-associated nephrotoxicity.

Material and methods

Study population

We conducted a prospective observational study in a cohort of patients with sUTI caused by XDR *P. aeruginosa* treated with intravenous CMS for at least 48 h. The study was carried out at Hospital del Mar, a university tertiary care hospital in Barcelona (Spain), from January 2010 to September 2014. The local ethics committee (Comité Ètic d'Investigació Clínica del Parc de Salut Mar) approved the study. Exclusion criteria were <18 years old, pregnancy, breast feeding during the study period, to have another concomitant infection focus or to be on renal replacement therapy. A pharmacy-generated alarm system was used to identify patients being treated with CMS for UTI. The study investigators performed the assessment from the first day of the treatment and informed consent was obtained from all participants or their legal representatives.

Collected data

Patient data collected included demographic information, Charlson comorbidity index,²² the severity of disease at the time of the first CMS dose stratified according to the Acute Physiology and Chronic Health Evaluation (APACHE II),²³ clinical status at the start of treatment (defined as infection, severe sepsis or shock according to standard definitions),²⁴ and CMS treatment (indication, daily and total cumulative dose measured in millions of international units (IU) and duration of treatment). Other clinical data included the presence of baseline chronic kidney disease (CKD, defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m² for ≥ 3 months), serum creatinine concentration, GFR at baseline and the end of treatment (EOT), calculated using the abbreviated Modification of Diet in Renal Disease equation (MDRD-4),²⁵ and the development of acute kidney injury (AKI) at EOT according to the RIFLE criteria.²⁶

Combination therapy with other antibiotics that had potential activity or synergy with colistin was assessed. These combinations included colistin plus meropenem (synergistic in vitro against the most prevalent strain in our center), ceftazidime or amikacin (potential activity against *P. aeruginosa*). Information was collected on the concomitant use of other nephrotoxic drugs (aminoglycosides, vancomycin, angiotensin II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, intravenous dye, amphotericin B and non-steroidal anti-inflammatory drugs (NSAIDs)), as well as the need for vasopressor drugs or discontinuation of CMS due to nephrotoxicity. Since this study was performed in patients with XDR *P. aeruginosa* infections, when vancomycin was used it was as part of an empirical treatment in patients with febrile neutropenia. Vancomycin was withdrawn when the diagnosis of UTI was performed.

Definitions

XDR was defined according to Magiorakos et al.²⁷, as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, antipseudomonal fluorquinolones, antipseudomonal penicillins + β -lactamase inhibitors, monobactams, phosphonic acids, polymyxins). UTI was defined when the patient presented with at least one of the following urinary tract symptoms: fever > 38 °C in patients ≤ 65 years of age, suprapubic tenderness, costovertebral angle pain or tenderness, urinary frequency, urinary urgency or dysuria, plus positive urinary culture with no more than two species of microorganisms identified and at least one of which had a colony count of ≥ 10⁵ CFU/mL.²⁸ Three UTI syndromes were considered:

1. Cystitis: the presence of dysuria and increased urinary frequency or urgency, with or without hematuria, in patients without fever (axillary temperature < 37.5 °C).
2. Pyelonephritis: presence of fever (axillary temperature ≥ 38 °C) and back pain or costovertebral angle tenderness.

Clinical failure was defined as when the patients showed no improvement or at least one of the initial symptoms, worsened or died. Clinical cure was defined as either the absence of symptoms or as a consistent improvement in the signs and symptoms of the infection. Bacteriological clearance and failure were defined as the eradication and persistence, respectively, of the previously isolated microorganism in a follow-up culture at the end of antibiotic treatment.

CMS administration

The dosage regimen and dose adjustments of CMS were determined by the responsible clinician. Each CMS dose (colistimethate

formulation for intravenous use, GES Genéricos Españoles®) was diluted in 100 mL of physiological saline and intravenously administered over 30 min. Each vial contained 1 million international units (IU) of CMS (equivalent to 80 mg CMS).

Microbiological data

Identification and susceptibility testing of *P. aeruginosa* were first performed by microdilution using the Gram-negative breakpoint panel for non-fermenting gram-negative bacteria of the MicroScan® WalkAway system (Siemens Diagnostic Inc., CA). Colistin minimal inhibitory concentration (MIC) was determined by microdilution using cation-adjusted MHB; the isolate was considered susceptible if the MIC was ≤ 2 mg/L according to the Clinical and Laboratory Standards Institute (CLSI).²⁹

Pharmacokinetic data

Blood samples were obtained just before the next dose on day 3–4 of the treatment. It was assumed that steady state had already been achieved considering a half-life for colistin of approximately 14 h.³⁰ Concentrations of CMS and formed colistin in plasma were measured using a validated HPLC method.^{31,32} The limit of quantification of the HPLC methods for colistin and CMS in plasma were 0.20 and 0.50 mg/L, respectively. Considering the 'flat' plasma concentration-time profiles of formed colistin in critically-ill patients,^{10,21} measured colistin concentrations were regarded as $C_{ss,avg}$. Consequently, AUC_{24h} in plasma was calculated by multiplying the obtained $C_{ss,avg}$ value by 24 h. Since the most predictive PK/PD index for colistin is the area under unbound plasma concentration vs time curve to the minimum inhibitory concentration ($fAUC/MIC$),³² we also calculated the $fAUC/MIC$ for each patient using 0.5 as the unbound fraction for colistin in human plasma.³²

Based on recent pharmacokinetic studies in critically ill patients,^{21,33} we also considered C_{ss} of 2.5 mg/L as the concentration target to guide therapy. We also analyzed the percentage of patients that achieved $AUC/MIC \geq 60$ mg.h/L for the target of infections caused by *P. aeruginosa*.²¹

The $C_{ss,avg}$ achieved by our patients in clinical practice were compared with those that would have been obtained if the recommended CMS dosing algorithm of Nation et al. would have been used.³⁴

Statistical analysis

Dichotomous data were compared using a χ^2 or Fisher's exact test. Normally distributed continuous data are expressed as means and standard deviations (SD), and compared using *t*-test. Otherwise, values are presented as means with interquartile range (IQR) and compared using the Mann-Whitney *U* test. Baseline and clinical characteristics of patients receiving different CMS doses were compared using ANOVA or Kruskal-Wallis test. Multivariate analysis of risk factors for colistin-associated nephrotoxicity was conducted using logistic regression. Univariate analyses were performed separately for each of the risk factor variables to ascertain the odds ratio (OR) and 95% confidence interval (CI). All clinically important covariates and those with a $p < 0.2$ in univariate analyses were included in the multivariate analysis.

Results

During the study period, 33 patients with sUTI caused by XDR *P. aeruginosa* treated with CMS were included. Patients' characteristics are summarized in Table 1. Sixteen (48.5%) patients had a urinary catheter at the time of infection and there were two patients (6.1%) with an indwelling urinary catheter. All catheters

Table 1
Characteristics of included patients.

	Patient (n = 33)
Age, years**	65.1 ± 13.1
Male sex, n (%)	26 (78.8)
^a APACHE II**	10.4 ± 6.83
Charlson score**	4.90 ± 2.8
Urinary catheter	16 (48.5)
UTI syndrome:	
- Cystitis	24 (72.7)
- Pyelonephritis	9 (27.3)
Positive blood cultures	4 (12.1)
Clinical status:	
- Sepsis, n (%)	10 (30.3)
- Shock, n (%)	1 (3.0)
^b CMS daily dose (million IU)**	5 ± 2.54
CMS daily dose (in colistin base activity, (mg)/kg/day)	2.21 ± 1.25
^b CMS total cumulative dose (million IU)*	24 (14.2–39.7)
^b CMS treatment duration, days**	8.31 ± 6.43
^c GFR at baseline (mL/min/1.73 m ²)**	100.2 ± 64.1
Patients with ^d CKD at baseline, n (%)	8 (24.2)
^e $C_{ss,avg}$ (mg/L)**	1.19 ± 1.09
^f AUC/MIC **	60.5 ± 56.4
^f $fAUC/MIC$ **	30.2 ± 28.2
^g $AUC/MIC \geq 60$ mg ^h /L, n (%)	11 (33.3)
^e % patients with $C_{ss,avg} > 2.5$ mg/L	3 (9.1)
^g Expected $C_{ss,avg}$	0.78 ± 0.07
$C_{ss,avg}$ above MIC	22 (66.7)
Combined antibiotic therapy:	14 (42.4)
- Meropenem	6 (18.2)
- Amikacin	3 (9.1)
- Ceftazidime	5 (15.2)
^h AKI at the end of treatment, n (%)	10 (30.3)
- R (Risk)	3 (30)
- I (Injury)	5 (50)
- F (Failure)	2 (20)
Clinical cure, n (%)	31 (93.9)
Microbiological follow up, n (%)	23 (69.7)
Microbiological clearance, n (%)	19/23 (82.6)

* Median (interquartile range).

** Mean ± standard deviation.

^a APACHE II: Acute Physiology and Chronic Health Evaluation II;

^b CMS: colistin methanesulfonate;

^c GFR: glomerular filtration rate;

^d CKD: chronic kidney disease;

^e $C_{ss,avg}$: colistin plasma concentration at steady-state;

^f AUC : colistin area under the curve;

^g Calculated $C_{ss,avg}$ according the dosage algorithm of Nation et al.;

^h AKI: acute kidney injury.

were removed or exchanged two days after an effective antibiotic treatment was started. Fever was present in 45.5% of the cases at the time of infectious diagnosis. However, blood cultures were only performed in 19 (57.6%) patients being only four (21.1%) positive. It's important to point out that 14 (42.4%) of patients in this cohort received combined antibiotic treatment (33.3% of patients with lower UTI and 66.7% of patients with acute pyelonephritis).

Colistin MIC of the most predominant *P. aeruginosa* strain in our hospital was 0.5 mg/L (24 isolates with a MIC of 0.5 mg/L, 8 isolates with a MIC of 0.25 mg/L, and 1 isolate with a MIC of 2 mg/L). The MIC₅₀ and MIC₉₀ values for colistin were 0.5 and 2 mg/L respectively. This strain displayed a ceftazidime MIC of 16 mg/L, an amikacin MIC of 16 mg/L and a meropenem MIC ≥ 8 mg/L.

CMS doses were administered as follows: 9 (27.3%) patients received 1 million IU three times a day (TID); 12 (36.4%) patients received 2 million IU TID; 3 (9.1%) patients received 3 million IU TID; 3 (9.1%) patients received 4.5 million IU two times a day (BID); and in 6 (18.2%) patients different dosage adjustments were made based on patients' renal function.

The mean plasma colistin C_{ss} was 1.19 mg/L, but individual values varied widely (0.21–5.20 mg/L) with the different selected doses. Only 3 (9.1%) patients showed colistin plasma concentrations > 2.5 mg/L and only 11 (33.3%) achieved an optimal PK/PD

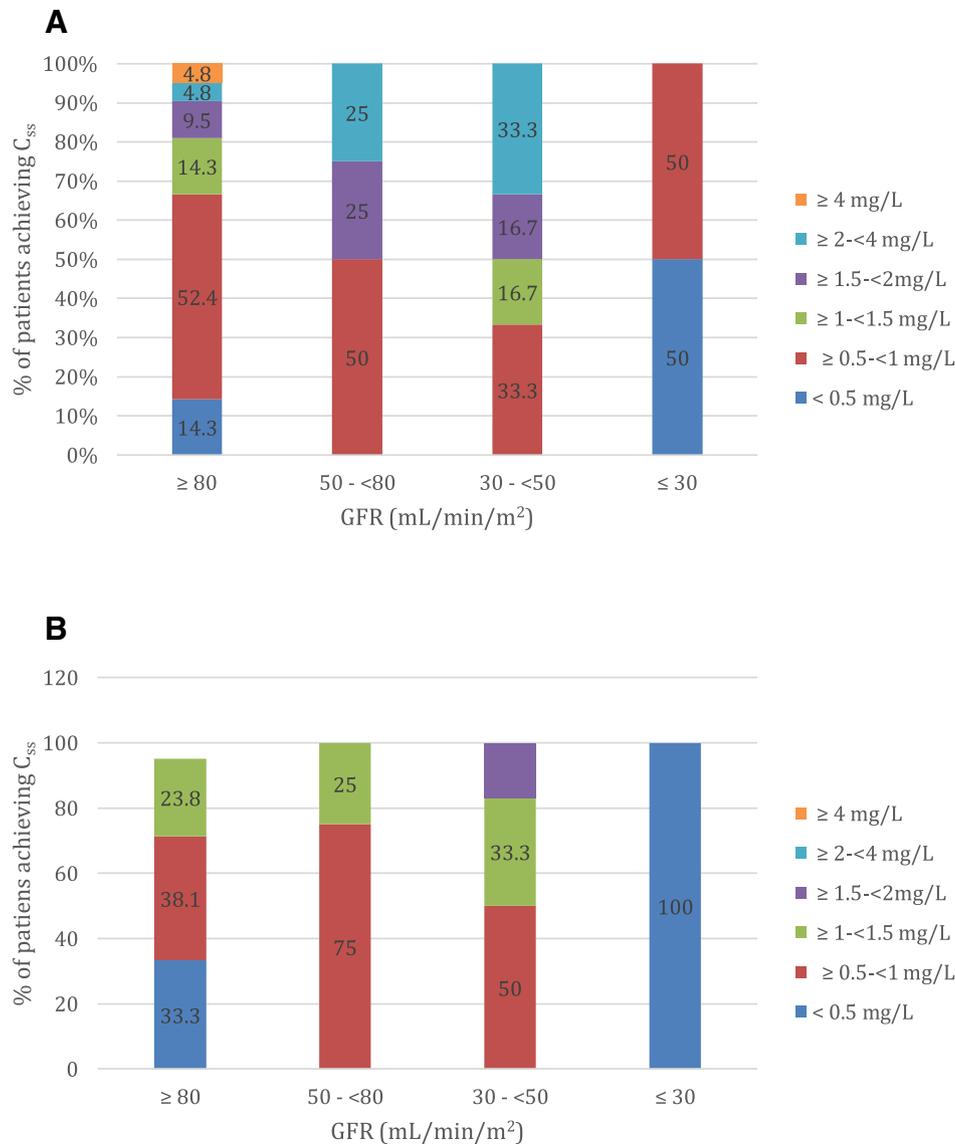


Fig. 1. Figure A and B shows the percentage of patients with different degrees of renal function achieving average steady-state plasma concentrations of colistin ($C_{ss,avg}$) of <0.5, ≥0.5-<1, ≥1, ≥1.5-<2, ≥2-<4, ≥4 mg/L using the real daily CMS dose selected by the responsible physician (A) and by applying the formula of Nation et al. (B)³⁴.

index ($AUC/MIC \geq 60$). If we consider the cut-off point for the $C_{ss,avg}$ of 2 mg/L (corresponding to an $AUC/MIC = 48$ mg·h/L) which has been recently recommended by Nation et al.^{34,35}, 5 (15.2%) patients achieved the therapeutic goal. However, it is important to point out that 22 (66.7%) patients showed colistin plasma concentrations above the MIC of the isolated *P. aeruginosa*.

Fig. 1 shows the percentage of patients with different renal function achieving the average C_{ss} of < 0.5, ≥ 0.5 to < 1, ≥ 1 to < 1.5, ≥ 1.5 to < 2, ≥ 2 to < 4, ≥ 4 mg/L with the dosage regimens chosen by the responsible physician. We observed that the median values of C_{ss} achieved by our patients are quite similar to those expected by applying the dosing CMS algorithm of Nation et al.³⁴ (0.84 [0.21–5.2] mg/L vs 0.7 [0.03–1.66] mg/L; $P = 0.26$).

Table 2 summarizes characteristics of the study participants according to the CMS dosage regimen. CMS dosage regimens were classified in four groups as follows: < 3 million IU/day, ≥ 3 million IU/day, ≥ 6 million IU/day and ≥ 9 million IU/day. No differences were observed in any of the demographic and clinical variables with the exception of the baseline GFR that was lower in patients that received the lowest dose of CMS. No correlation was observed

between $C_{ss,avg}$ and GFR (Spearman rho, -0.07 ; $P = 0.63$) or CMS daily dose (Spearman rho, 0.30 ; $P = 0.09$).

Table 3 shows the characteristics of patients with and without clinical cure in the total cohort and in the group of patients treated with colistin monotherapy. In the entire cohort, clinical cure was achieved in 31 (93.9%) patients. Within patients with clinical cure, only 10 (32.3%) achieved an $AUC/MIC > 60$ mg·h/L and only 2 (6.5%) a $C_{ss,avg} > 2.5$ mg/L. In the group treated with colistin monotherapy, clinical cure was achieved in 17 of the 19 (89.5%) patients. Of these, only 5 (29.4%) attained an optimal AUC/MIC and only 1 (5.9%) the therapeutic level of formed colistin.

At this point, we also analyzed patients with clinical failure, and we found that they were those who died of other comorbidities but not attributable to the UTI.

Despite the small sample size, we performed an analysis on the 9 patients diagnosed with pyelonephritis. All of them achieved clinical cure even though none of them reached a $C_{ss,avg}$ above 2.5 mg/L and only 1 (11.1%) achieved an $AUC/MIC > 60$ mg·h/L. However, it is important to note that six (66.7%) of them were treated with combined therapy.

Table 2
Clinical and demographic characteristics of patients receiving different CMS dosage regimens.

Variable	< 3 million IU/day (n = 6)	≥ 3 million IU/day (n = 9)	≥ 6 million IU/day (n = 12)	≥ 9 million IU/day (n = 6)	P
Age, years**	76 (70–85)	67 (44–82)	61 (46–77)	69 (52–85)	0.06
Male sex, n (%)	6 (100)	8 (88.9)	8 (66.7)	4 (66.7)	0.08
Charlson index**	8 (4–9)	5 (0–9)	4 (0–9)	6 (2–7)	0.3
Clinical status:					
- Severe sepsis	2 (33.3)	3 (33.3)	3 (25)	2 (33.3)	0.86
- Shock	1 (16.7)	0 (0)	0 (0)	0 (0)	0.18
^a CMS total dose (million IU) *	20 (4–40)	24 (9–112)	24 (11–120)	30 (27–99)	0.20
^a CMS treatment duration, days**	10 (5–20)	8 (3–28)	5 (3–20)	5 (3–11)	0.62
^b GFR at baseline (mL/min/1.73 m ²)**	33.4 (19–51)	96.9 (39–353)	107 (44–212)	122 (81–138)	0.005
^c C _{ss,avg} (mg/L)**	0.85 (0.28–3.02)	0.57 (0.21–2.43)	1.1 (0.5–3.64)	1.4 (0.3–5.2)	0.16
^d Expected C _{ss,avg} (mg/L)	0.51 (0.35–0.62)	0.46 (0.03–1.17)	0.83 (0.26–1.65)	1.04 (0.88–1.66)	0.05
^e AUC/MIC**	40.8 (12–145)	27.4 (9.6–116.6)	42.7 (15.6–174.7)	67.2 (57.6–249.6)	0.21
AUC/MIC > 60 mg·h/L	2 (33.3)	1 (11.1)	5 (41.7)	3 (50)	0.37
C _{ss,avg} > 2.5 mg/L	1 (16.7)	0 (0)	1 (8.3)	1 (16.7)	0.83
C _{ss,avg} above MIC	3 (50)	6 (66.7)	9 (75)	4 (66.7)	0.61
^g AKI at ^g EOT, n (%):	2 (33.3)	3 (33.3)	4 (33.3)	1 (16.7)	0.89
- R (Risk)	1 (50)	0 (0)	1 (25)	0 (0)	
- I (Injury)	1 (50)	2 (66.7)	3 (75)	0 (0)	
- F (Failure)	0 (0)	1 (33.3)	0 (0)	1 (100)	
Clinical cure, n (%)	6 (100)	8 (88.9)	11 (91.7)	6 (100)	0.95
Microbiological eradication, n (%)	2/4 (50)	7/8 (87.5)	7/8 (87.5)	3/3 (100)	0.36

^a CMS: colistin methanesulfonate;

^b GFR: glomerular filtration rate;

^c C_{ss,avg}: colistin plasma concentration at steady-state;

^d Calculated C_{ss,avg} according to the algorithm of Nation et al.;

^e AUC: colistin area under the curve;

^f MIC: minimum inhibitory concentration;

^g AKI: acute kidney injury.

Microbiological follow up was available in 23 patients of whom 19 (82.6%) accomplished microbiological clearance. Only 7/19 (36.8%) of these patients had reached an AUC/MIC of 60 mg·h/L and 2/19 (10.5%) a C_{ss,avg} ≥ 2.5 mg/L. No significant difference between patients who received colistin monotherapy and those who received combination therapy was observed for microbiological outcome (10/13 [76.9%] vs 9/10 [90%]; *p* = 1).

AKI at EOT was observed in 10 (30.3%) patients. The univariate analysis of risk factors for AKI showed significant differences for the Charlson score and C_{ss,avg} and a trend in the use of loop diuretics (Table 4). However, in the multivariate analysis only the Charlson score (odds ratio (OR) 1.55 (95% confidence interval (CI): 0.95–2.45, *P* = 0.081) and C_{ss,avg} (OR 4.36 (95% CI: 0.86–20, *P* = 0.074) showed a trend towards statistical significance (Table 5). There were no differences between patients treated with colistin and those treated with combined antibiotic therapy (6/19 [31.6%] vs 4/14 [28.6%]; *p* = 1).

Discussion

The aim of this study was to assess the plasma AUC/MIC values of formed colistin in a cohort of patients with UTI caused by XDR *P. aeruginosa* treated with intravenous CMS, and the association with clinical and microbiological outcomes. Although only 11 (33.3%) patients achieved the optimal plasma PK/PD target (AUC/MIC ≥ 60 mg·h/L), the clinical cure rate was 93.9% with 82.6% microbiological eradication rate. When the data were analyzed based upon colistin plasma concentration of 2.5 mg/L as a therapeutic target, no relationship was observed between the PK data and clinical outcomes, as only 6.5% of the cured patients achieved this target.

In recent clinical studies, the rate of clinical cure in UTI caused by MDR-GNB treated with CMS ranged from 50 to 92%.^{36–38} Zaidi et al. performed a retrospective study of 155 patients with infections caused by MDR GNB treated with low-dose colistin (1.9 mg/kg/day of colistin base activity (CBA) [i.e. 0.063 IU/kg/day] in patients with clinical cure vs 1.7 mg CBA/kg [i.e. 0.057 IU/kg/day] in patients without clinical cure).³⁶ In that study, the clinical cure

rate in patients diagnosed with UTI was 83.3%.³⁶ Cheng et al. performed another retrospective study including patients diagnosed with MDR-GNB and treated with CMS, in whom only 5 out of 10 (50%) patients with UTI achieved clinical cure.³⁷ Dosage regimens of CMS in the Cheng study were based on the patient's creatinine clearance (CL_{cr}) as follows: CL_{cr} ≥ 80 mL/min, 5.0 mg CBA/kg/day; CL_{cr} 30–79 mL/min, 2.5–3.8 mg CBA/kg/day; and CL_{cr} < 30 mL/min, 2.5 mg CBA/kg/day.³⁷ A previous cohort study published by our group included 13 patients with UTI caused by XDR *P. aeruginosa* and treated with CMS, and reported 84.6% of clinical cure.³⁸ In our study the average of CMS daily dose was 3 million IU per day (i.e. 1.42 mg CBA/kg/day in a patient with approximate body weight of 70 kg). Most recent clinical experience confirmed that intravenous CMS is an effective option for the treatment of UTI caused by MDR-GNB, even when it is administered at low doses. However, the limitations of most previous studies include a limited sample size, a wide range of CMS daily doses, antibiotic combination therapy and lack of pharmacokinetic data; therefore, it is difficult to draw conclusions about the optimal CMS dosage regimens for treating UTI.

In the present study, only 6 patients (18.2%) received the highest approved daily dose of CMS (i.e. 9 million IU) and 6 (18.2%) received the lowest recommended dose (i.e. < 3 million IU). These data confirm that despite recent recommendation of regulatory agencies³⁹ and those derived from modern population pharmacokinetic studies,³⁴ physicians are still using outdated product or hospital CMS dosing recommendations, probably because their concern about nephrotoxicity. Nevertheless, no differences were observed in the clinical cure rate between patients receiving different CMS doses.

A key finding of this study is that the achieved C_{ss,avg} in daily clinical practice in our hospital was low. In fact, only 9% of patients achieved the therapeutic goal of C_{ss,avg} (i.e. 2–0.5 mg/L) and only 33.3% the optimal PK/PD index (i.e. AUC/MIC ≥ 60 mg·h/L). This finding is consistent with our previous studies.^{10,40} Moreover C_{ss,avg} achieved in this cohort match with the results of C_{ss,avg} expected by applying equation proposed by Nation et al.³⁴ indicating that higher doses of CMS are required if higher C_{ss,avg} are needed

Table 3
Characteristics of patients according to the clinical outcome.

Variable	Included patients			Patients treated with colistin alone		
	Clinical cure (n=31)	Clinical failure (n=2)	P	Clinical cure (n=17)	Clinical failure (n=2)	P
Age, years	69 (44–85)	72.5 (72–73)	0.5	68.5 (46–85)	72.5 (72–73)	0.35
Male sex, n (%)	24 (77.4)	2 (100)	1	14 (82.4)	2 (100)	1
Charlson	5 (0–9)	6.5 (4–9)	0.42	4.5 (0–9)	6.5 (4–9)	0.35
APACHE II	8.5 (2–28)	11.5 (9–14)	0.44	8.5 (2–28)	11.5 (9–14)	0.64
Clinical status:						
- Severe sepsis	10 (32.3)	0 (0)	1	12 (70.6)	2 (100)	1
- Shock	1 (3.2)	0 (0)	1	0 (0)	0 (0)	1
Fever at start of colistin treatment, n (%)	15 (48.4)	0 (0)	0.49	9 (52.9)	0 (0)	0.47
UTI syndrome:						
- Cystitis	22 (71)	2 (100)	1	14 (82.4)	2 (100)	1
- Pyelonephritis	9 (29)	0 (0)		3 (17.6)	0 (0)	
CMS ^a daily dose (millions IU)	3.5 (1–9)	4.5 (3–6)	0.91	4 (2–9)	4.5 (3–6)	0.95
CMS ^a total dose (millions IU)	30 (12–120)	36 (24–48)	0.53	18 (6–39)	36 (24–48)	0.11
CMS ^a treatment duration, days	5 (3–28)	8	0.53	4 (3–10)	8	0.22
Colistin base activity (mg/kg/day)	1.76 (0.52–5.1)	2.43 (1.51–3.34)	0.9	2.27 (0.8–3.64)	2.42 (1.51–3.34)	0.89
GFR ^b at baseline (ml/min/1.73 m ²)	90.3 (19–334)	109.5 (97–122)	0.37	82.02 (33–353)	109.5 (97–122)	0.43
Patients with CKD ^c at baseline, n (%)	9 (29)	0 (0)	1	5 (29.4)	0 (0)	1
C _{ss,avg} ^d (mg/L)	0.84 (0.21–5.2)	1.98 (0.31–3.64)	0.85	0.7 (0.21–3.02)	1.98 (0.31–3.64)	0.69
C _{ss,avg} above MIC ^e	21 (67.7)	1 (50)	1	10 (58.8)	1 (50)	1
^f AUC/MIC	40.8 (9.6–249.6)	94.8 (14.9–174.7)	0.73	33.6 (9.6–163.2)	94.8 (14.9–174.7)	0.69
^f AUC/MIC	21.5 (5.04–124.8)	47.4 (7.44–87.4)	0.85	16.8 (4.8–81.6)	47.4 (7.44–87.4)	0.69
AUC/MIC ≥ 60 mg/L	10 (32.3)	1 (50)	1	5 (29.4)	1 (50)	1
C _{ss} > 2.5 mg/L	2 (6.5)	1 (50)	0.18	1 (5.9)	1 (50)	0.2
AKI ^g at end of treatment, n (%):	9 (29)	1 (50)	0.52	5 (29.4)	1 (50)	1

Data are n (%) except indicated or median (interquartile range).

^a CMS: colistin methanesulfonate;

^b GFR: glomerular filtration rate;

^c CKD: chronic kidney disease;

^d C_{ss}: colistin plasma concentrations at steady-state;

^e MIC: minimum inhibitory concentration;

^f AUC: area under the curve;

^g AKI: acute kidney injury.

Table 4
Univariate analysis of the characteristics of patients with and without nephrotoxicity at EOT.

	Patients with AKI (n=10)	Patients without AKI (n=23)	P
Male sex, n (%)	8 (80)	18 (78.3)	1
Age, years	72.5 (54–82)	65 (37–85)	0.11
Charlson index	7.5 (4–9)	4 (0–9)	0.008
APACHE II	8.5 (5–14)	9 (2–28)	0.88
Clinical status:			0.68
- Sepsis	2 (20)	8 (34.8)	
BMI ^a (Kg/m ²)	22.6 (15.5–31.3)	24.4 (21.1–30.12)	1
GFR ^b at baseline (ml/min/1.73 m ²)	96.9 (19–353)	79.9 (33–159)	0.6
^c CMS total dose (million IU)	22 (9–112)	25.5 (4–120)	0.9
CMS ^a treatment duration, days	6.5 (3–28)	6 (3–20)	0.9
Colistin base activity (mg)/kg/day	1.81 (0.85–5.10)	1.7 (0.52–3.4)	0.88
^d C _{ss,avg} (mg/L)	1.65 (0.7–5.2)	0.57 (0.21–2.42)	0.001
^e AUC/MIC ^f (mg/L)	96.7 (28.8–249.6)	27.4 (9.6–116.2)	0.007
^f AUC/MIC	48.4 (14.4–124.8)	13.7 (4.8–58.1)	
Concomitant aminoglycoside use, n (%)	3 (30.0)	3 (13.0)	0.45
Concomitant vancomycin use, n (%)	0 (0)	3 (13.0)	0.53
Concomitant use of loop diuretic, n (%)	5 (50.0)	4 (17.4)	0.09

Data are n (%) or median (interquartile range).

Median (interquartile range).

^a BMI: body mass index;

^b GFR: glomerular filtration rate;

^c CMS: colistin methanesulfonate;

^d C_{ss,avg}: colistin plasma concentrations at steady-state;

^e MIC: minimum inhibitory concentration;

^f AUC: area under the curve.

The influence of renal function and hence the CMS daily dose on the C_{ss,avg} of formed colistin could not be demonstrated in this study, probably due to the small sample size. However, this study confirms the wide interpatient variability,^{21,34} even at a given range of GFR and after receiving the same range CMS doses, there were approximately 10-fold variations in C_{ss,avg}.

Clinical cure was achieved in 93.9% of patients. It's important to highlight that among patients achieving clinical cure, only 2

(6.5%) had achieved colistin plasma concentrations ≥ 2.5 mg/L and only 10 (32.3%) had attained an optimal AUC/MIC in plasma of 60 mg·h/L. If we focus on the group of patients treated with colistin monotherapy, clinical cure was achieved in 89.5% of patients. In the same way, only 5 (29.4%) have attained an optimal AUC/MIC and only 1 (5.9%) the therapeutic level of formed colistin. However, it has to be considered that in almost 60% of all patients, the obtained C_{ss,avg} was above the MIC of the isolated *P.*

Table 5
Multivariate analysis of the risk factors for nephrotoxicity at EOT.

Variable	Odds ratio (95% CI)	P
Charlson score	1.55 (0.95–2.45)	0.081
C _{ss,avg}	4.36 (0.86–20)	0.074
Use of loop diuretics	0.69 (0.08–5.76)	0.735

aeruginosa, a fact probably related to the low MIC values of our isolates. Similar results were observed in the group of patients diagnosed with pyelonephritis since all of them were cured but none of them achieved the plasma concentration target and only 1 (11.1%), the optimal PK/PD index. Nevertheless, the fact that only 33.3% of them were treated with colistin monotherapy, prevent us from drawing consistent conclusions about the efficacy of this polymyxin in patients with pyelonephritis.

It is well known that the urinary recovery of CMS is high and CMS can be converted to colistin *in vivo*.¹⁸ In a pharmacokinetic study in young volunteers treated with a single dose of 1 million IU (80 mg) CMS, Couet et al. estimated that the rate of CMS conversion into colistin was only 30%.⁴¹ Importantly, in this study CMS was mainly excreted in urine (70% on average) and the conversion to colistin most likely occurred in the bladder.⁴¹ A recent pharmacokinetic study performed by our group demonstrated that in 11 of 12 (91.7%) patients treated with CMS, concentrations of formed colistin in urine (up to 95.4 mg/L) were much higher than those achieved in plasma (median (IQR): 0.9 mg/L [<0.2 –1.4 mg/L]) and the achieved colistin concentrations in urine were well above the MIC (0.5 mg/L) of the most predominant isolate of *P. aeruginosa* in our hospital.¹⁵ Regarding the MIC of the XDR *P. aeruginosa* reported in the present study, it is important to point out that it is lower compared with other studies. In a study of 785 clinical isolates of XDR *P. aeruginosa*, Sader et al. reported an MIC_{50/90} of 1/2 mg/L.⁴² In another study performed by the same group in 6091 bacterial isolates, MIC_{50/90} values were 1/1 mg/L.⁴³ Recently, a study performed in Spain reported MIC_{50/90} values of 2 mg/L.⁴⁴ In the present study, the high clinical cure rate obtained with suboptimal AUC/MIC values could be explained by the fact that a much higher colistin exposure was probably reached in the bladder and urinary tract than in plasma, but also to the low MIC of the XDR *P. aeruginosa*. Taken together, use of the targeted colistin AUC/MIC in plasma may be not suitable for predicting the efficacy of intravenous CMS in UTI patients and the measurement of concentrations of formed colistin in urine may be more useful. Clearly, urine samples should be collected on ice and analyzed as soon as possible to avoid any potential conversion of CMS to colistin during the sample collection procedure. In summary, our clinical experience in using intravenous CMS over the last decade supports the use of therapeutic drug monitoring (TDM) of colistin levels in plasma, as well as in urine in patients with UTI caused by XDR-GNB.

In the present study, microbiological clearance was 82.6% in the 23 patients that had microbiological follow up and no colistin-resistant isolates were detected during the next 30 days. The fact that microbiological clearance was a little lower than the clinical cure rate might be due to colonization of MDR GNB in the urinary tract of several patients. The prevalence of asymptomatic bacteriuria varies widely with age, gender and the presence of genitourinary abnormalities.⁴⁵ Patients with chronic disabilities or comorbidities characterized by impaired urinary voiding or with indwelling urinary devices are at high risk of asymptomatic bacteriuria, and in this scenario hospitalized patients are a group in which this medical condition is frequently present.

The rate of AKI at EOT in our series of patients was 30.3% and most of them were classified as “injury” by the RIFLE criteria. The reported rate of colistin-associated nephrotoxicity in recent

studies using the RIFLE criteria varied from 40–50%.^{46,47} In our multivariate analysis, the only factors that showed a trend towards statistically significance were the Charlson score and the C_{ss,avg}. The association between colistin plasma concentrations and nephrotoxicity has previously been reported by our group that demonstrated that C_{ss,avg} > 2.42 mg/L was associated with a higher risk of AKI at EOT.⁴⁶

The high clinical response rate observed in this study and the risk of colistin-associated nephrotoxicity highlights the need for routine therapeutic drug monitoring of colistin in daily clinical practice, in order to maximize clinical efficacy while minimizing the nephrotoxicity. In addition, the measurement of colistin plasma levels in urine could be a useful tool to examine if the exposure of colistin is sufficient at the site of infection. Unfortunately, current data on TDM of colistin in clinical practice are sparse,^{40,48} despite that it is strongly recommended by recent consensus documents.^{9,13,49,50} Currently, several new antimicrobial agents for the treatment of MDR and XDR *P. aeruginosa* such as ceftolozane-tazobactam and ceftazidime-avibactam are available in daily clinical practice. Overall these agents appear to be safer and more effective than colistin.⁵¹ However, resistance to ceftolozane-tazobactam and ceftazidime-avibactam emerged, in some cases, during treatment^{4,52,53} suggesting that there is still a need for the use of polymyxins and indicating that there will be a place for them in the future.

To the best of our knowledge, this is the largest study of UTI caused by XDR *P. aeruginosa* treated with intravenous CMS and the first clinical study assessing the relationship between colistin PK/PD target in plasma and clinical outcomes. Our study has several limitations, such as the small sample size and the fact that about 40% of the patients were treated with combined therapy, especially in patients with pyelonephritis. In addition, the lack of pharmacokinetic data in urine prevented us from calculating the AUC/MIC of formed colistin in urine. We suggest that using lower CMS doses than the currently recommended dosage regimens could be reasonable for the treatment of lower UTI caused by XDR *P. aeruginosa* with low colistin MIC values. This strategy could lead to lower rates of nephrotoxicity while maintaining the same effectiveness and minimizing the use of this last-line antibiotic. However, given that the microbiological clearance rate seems to be lower than the rate of clinical cure as several patients might have bacterial colonization in the urinary tract, caution is required with regard to the emergence of resistance with lower doses of CMS. Collectively, further prospective clinical studies are required and measuring colistin concentrations in urine is crucial for maximizing the efficacy of intravenous CMS against UTIs.

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Conflicts of interest

JPH has received grant from MSD, has participated in educational activities with MSD, Pfizer and Astellas and collaborated as advisor for Angelini, MSD Zambon, Shionogi and Pfizer. SG has participated in educational activities with Pfizer, Angellini, MSD and

Astellas. Other authors declare that they have no competing interests. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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