CRITICAL CARE

LETTER

Acute kidney injury: taking aim at colistin

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See related research by Rocco et al., http://ccforum.com/content/17/4/R174

We appreciate the contribution of Rocco and colleagues [1], whose retrospective study in a recent issue of *Critical Care* evaluated risk factors for acute kidney injury (AKI) in patients receiving colistin methanesulfonate (CMS) or other nephrotoxic antimicrobials. The following key thoughts occurred to us after reviewing the study.

We would like to address the criteria the authors used to qualify AKI. The authors note using RIFLE (Risk, Injury, and Failure; and Loss, and End-stage kidney disease) criteria to assess kidney injury, and note the degree of increase of serum creatinine from baseline in categorizing patients. However, the authors do not comment on urine output in these patients. Both urine output and serum creatinine are critical variables in recognizing kidney injury in a timely manner [2].

As noted, the literature on CMS pharmacokinetics is limited. A recent study investigating the pharmacokinetics of colistin noted that the maximum plasma concentration-to-minimum inhibitory concentration was much lower for *Pseudomonas* species than for other Gram-negative rods [3]. This implies that higher doses of CMS, and potentially more nephrotoxic doses, are required for treating *Pseudomonas* infections. Additionally, for those patients receiving continuous renal replacement therapy, the effective dose of antibiotic received may vary. It would be interesting to see what relationship, if any, exists between AKI and targeted bacteria species in critically ill patients on CMS.

We appreciate the contribution of the authors to the literature on the prediction of AKI in critically ill patients receiving nephrotoxic antimicrobials. Further investigations into both the efficacy and potential harm of this antimicrobial are warranted.

Abbreviations
AKI: Acute kidney injury; CMS: Colistin methanesulfonate.

Competing interests
The authors declare that they have no competing interests.

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CRITICAL CARE

RESEARCH Open Access

Risk factors for acute kidney injury in critically ill patients receiving high intravenous doses of colistin methanesulfonate and/or other nephrotoxic antibiotics: a retrospective cohort study

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Abstract

Introduction: Use of colistin methanesulfonate (CMS) was abandoned in the 1970s because of excessive nephrotoxicity, but it has been reintroduced as a last-resort treatment for extensively drug-resistant infections caused by gram-negative bacteria (*Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumonia*). We conducted a retrospective cohort study to evaluate risk factors for new-onset acute kidney injury (AKI) in critically ill patients receiving high intravenous doses of colistin methanesulfonate and/or other nephrotoxic antibiotics.

Methods: The cohort consisted of 279 adults admitted to two general ICUs in teaching hospitals between 1 April 2009 and 30 June 2011 with 1) no evidence on admission of acute or chronic kidney disease; and 2) treatment for more than seven days with CMS and/or other nephrotoxic antimicrobials (NAs, that is, aminoglycosides, glycopeptides). Logistic regression analysis was used to identify risk factors associated with this outcome.

Results: The 279 cases that met the inclusion criteria included 147 patients treated with CMS, alone (n = 90) or with NAs (n = 57), and 132 treated with NAs alone. The 111 (40%) who developed AKI were significantly older and had significantly higher Simplified Acute Physiology Score II (SAPS II) scores than those who did not develop AKI, but rates of hypertension, diabetes mellitus and congestive heart failure were similar in the two groups. The final logistic regression model showed that in the 147 patients who received CMS alone or with NAs, onset of AKI during the ICU stay was associated with septic shock and with SAPS II scores ≥43. Similar results were obtained in the 222 patients treated with CMS alone or NAs alone.

Conclusions: In severely ill ICU patients without pre-existing renal disease who receive CMS high-dose for more than seven days, CMS therapy does not appear to be a risk factor for this outcome. Instead, the development of AKI was strongly correlated with the presence of septic shock and with the severity of the patients as reflected by the SAPS II score.

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Introduction

Throughout the world, *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Klebsiella pneumonia* have emerged as major causes of nosocomial infections [1], particularly in patients who are critically ill and/or immunocompromised. Concern has been raised by reports of a stepwise trend towards extensive drug-resistance in these organisms [1]. Infections caused by extensively drug-resistant (XDR) bacterial strains are associated with high mortality rates, especially in intensive care units (ICUs), where outbreaks are extremely difficult to control. The limited therapeutic options in these cases often lead clinicians to resort to salvage therapy with colistin methanesulfonate (CMS). This older polymyxin antibiotic, which is converted *in vivo* to colistin [2], was widely abandoned in the 1970s because of its unfavorable pharmacokinetic properties and frequent adverse effects, particularly nephrotoxicity.

The "modern polymyxin era" [3], which began in the late 1990s, is characterized by a variety of dosing schedules, but to date there is still a dearth of information on the clinical pharmacokinetics of CMS and colistin in critically ill patients [4]. Higher doses appear to be beneficial in these cases [5], but it is unclear whether the improved efficacy comes at a cost of increased toxicity. The aim of this retrospective cohort study was to evaluate the potential risk factors for acute kidney injury (AKI), as defined by the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage kidney disease) classification system [6], in severely ill ICU patients without pre-existing renal disease who received high-dose intravenous CMS therapy for more than seven days.

Materials and methods

This study was conducted in two large tertiary-care teaching hospitals in Rome, Italy (Policlinico Umberto I and the Policlinico Gemelli), and it involved retrospective analysis of prospectively collected data. Cases were identified through searches of the ICU patient databases, and data were collected from the patients' electronic medical records.

The study cohort consisted of adults (≥18 years) consecutively admitted to the general ICUs of the participating facilities between April 2009 and June 2011 (Figure 1). Inclusion criteria were: 1) no evidence on ICU admission - as well as at protocol admission - of chronic renal failure and normal estimated glomerular

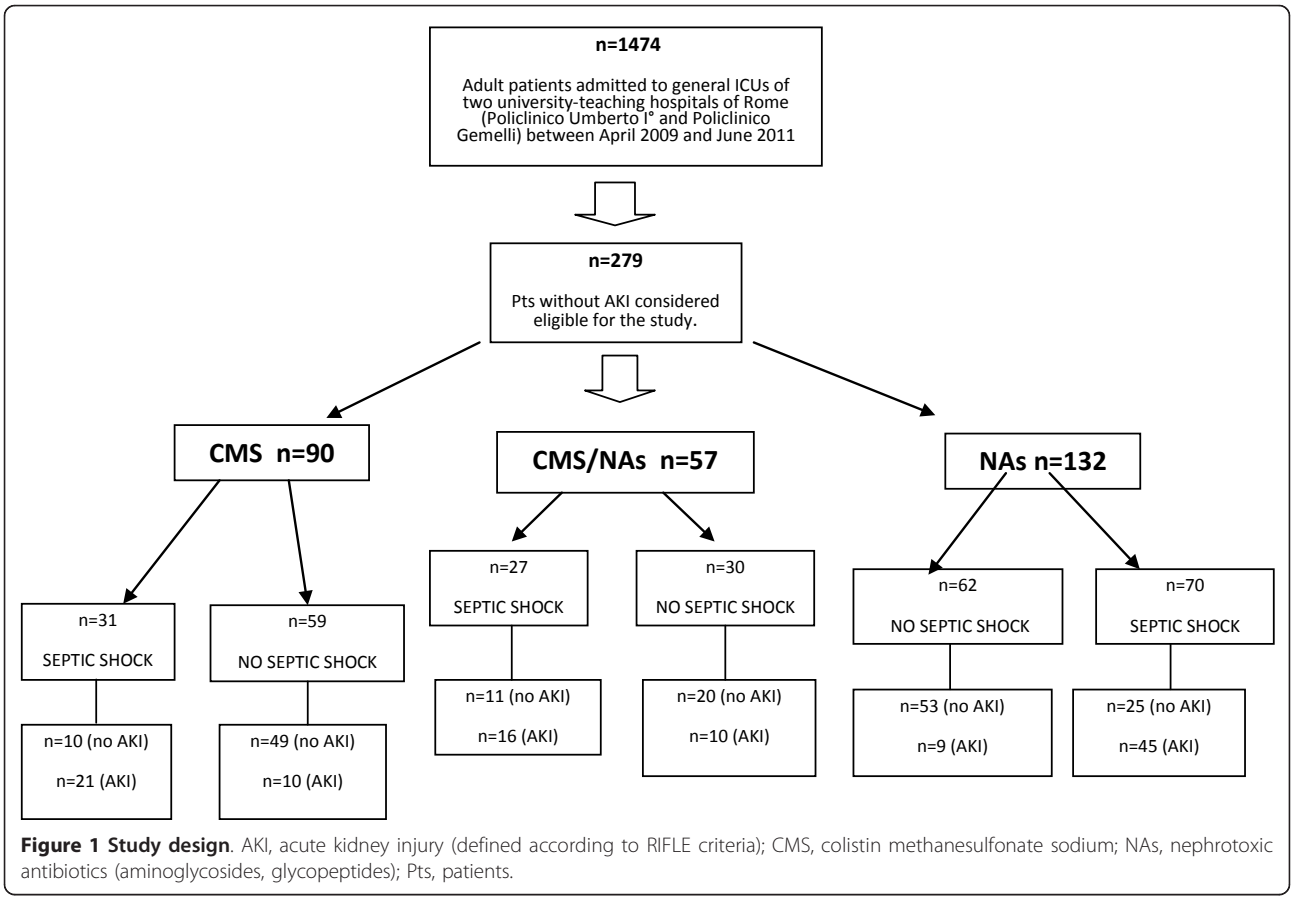

Figure 1 Study design. AKI, acute kidney injury (defined according to RIFLE criteria); CMS, colistin methanesulfonate sodium; NAs, nephrotoxic antibiotics (aminoglycosides, glycopeptides); Pts, patients.

filtration rate (GFR) relative to serum creatinine (SCr) based on age, race and sex formula assuming a glomerular filtration rate of 75 mL/min/1.73 m^2, as recommended by the Acute Dialysis Quality Initiative (ADQI) Working Group [6]. Most ICU patients, in fact, have not a prior measure of renal function and a simplified modification of diet in renal disease (MDRD) formula provides a simple and precise estimation of baseline GFR and SCr 2) onset ≥48 h after ICU admission of an XDR bacterial infection treated for seven or more days with intravenous (iv) CMS and/or other nephrotoxic antimicrobial agents (NAs, that is, aminoglycosides and glycopeptides).

Extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (that is, bacterial isolates remain susceptible to only one or two categories) [7]. Patients were excluded if the antibiotic therapy described above had been started prior to ICU admission.

The primary end point of the study was to evaluate the potential risk factors for acute kidney injury (AKI) in severely ill ICU patients without pre-existing renal disease who received high-dose intravenous CMS therapy with or without other nephrotoxic antimicrobials.

For this purpose, patients were classified daily using the RIFLE criteria and AKI was defined using the serum creatinine compared to the baseline value of the SCr previously obtained from the MDRD equation.

A patient was considered to have AKI when he had an increase in SCr of at least 50% from baseline (defined as Risk) or if he doubled the SCr level from the baseline (defined as Injury) or had a three times increase in SCr (defined as Failure) [6,8] (Figure 2).

For each patient included in the cohort, electronic hospital charts were reviewed, and the following collected data were recorded: demographic variables; Simplified Acute Physiology Score II (SAPS II); presence on admission of hypertension, diabetes mellitus, and/or congestive heart failure; reason for ICU admission; length of ICU stay; type and cause of infection; nephrotoxic drugs and iv iodate contrast used, immunocompromised status; albumin serum level, bilirubin serum level and, for CMS, duration of therapy and cumulative doses; presence of septic shock caused by the XDR infection; use of continuous renal replacement therapy (CRRT) during the ICU stay and ICU mortality.

Septic shock was diagnosed as a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate fluid resuscitation or by tissue hypoperfusion in the presence of proven or suspected infection [9]. Bloodstream infection (BSI) was defined as at least one positive blood culture for a potential bacterium together with clinical features compatible with systemic inflammatory response syndrome; the clinical suspicion of pneumonia was based on either clinical criteria (new or progressive radiologic pulmonary infiltrate together with at least two of the following: temperature >38°C or <36°C, leukocytosis >12,000/mL or leucopoenia <4,000/mL, or purulent respiratory secretions) or a simplified Clinical Pulmonary Infectious Score greater than or equal to six points. The microbiologic evaluation included the collection of at least one lower respiratory airway sample by tracheobronchial aspirates, bronchoscopic or blind bronchoalveolar lavage, within the first 24 hours of the onset of symptoms. Microbiologic confirmation of pneumonia was defined by the presence of at least one potentially pathogenic microorganism in respiratory samples above predefined thresholds bronchoalveolar lavage $>10^4$, and sputum or tracheobronchial aspirates $>10^5$ colony-forming units/ml, respectively [10,11].

CLASS	GFR CRITERIA	URINARY OUTPUT CRITERIA
RISK	Serum creatinine × 1.5 or GFR decrease >25%	<0.5 ml/kg/h × 6 h
INJURY	Serum creatinine × 2 or GFR decrease >50%	<0.5 ml/kg/h × 12 h
FAILURE	Serum creatinine × 3, or GFR decrease >75% Serum creatinine ≥4 mg/d with an acute rise >0.5 mg/dl	<0.3 ml/kg/h × 24 h, or anuria 12 h
LOSS	Persistent acute renal failure = complete loss of kidney function >4 weeks	
END-STAGE KIDNEY DISEASE	End-stage kidney disease >3 months	

Figure 2 RIFLE classification. Patients are classified on serum creatinine or urinary output, or both, the worst parameters are used. Glomerular filtration rate (GFR) criteria are calculated as an increase of serum creatinine above the baseline serum creatinine level. When the baseline serum creatinine is unknown and there is no past history of chronic kidney disease, serum creatinine is calculated using the Modification of Diet in Renal Disease formula for assessment of kidney function assuming a GFR of 75 ml/min/1.73 m^2. RIFLE, Risk Injury-Failure-Loss-End-stage kidney disease.

This study was approved by our institutional review board that waived the need for informed consent, due to the retrospective design of this study.

Statistical analysis

MedCalc software, version 12.1.0 (MedCalc® Software v 12.2.1, MariaKerke, Belgium) was used for all statistical analyses. Differences between groups were assessed with the Mann-Whitney test and results given as medians and interquartile ranges (IQR). The Kolmogorov-Smirnov test was used to assess variable distribution. Categorical variables, presented as proportions, were analyzed with the chi-square test or Fisher's exact test, as appropriate. *P*-values of <0.05 were regarded as significant. Potential risk factors for AKI were identified by means of univariate analysis with calculation of crude odds ratios (ORs). Those that emerged from this analysis with a *P*-value of <0.2 were candidates for inclusion in the multivariate model. The variables included in the final predictive model were selected with a stepwise procedure, and the accuracy of the model was assessed in terms of the area under the receiver operating characteristic (ROC) curve.

Results

Between April 2009 and June 2011, 1,474 adult patients were consecutively admitted to the two participating ICUs, and 279 (19%) of these met the criteria for inclusion in the study (Figure 1). Their characteristics are reported in Tables 1 and 2. The NAs patients were older, had a longer ICU stay and had a higher percentage immunocompromised than the other groups; the number of NAs patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) were statistically significant in respect to the CMS group (Table 1).

One hundred thirty-two of the patients received intravenous therapy with NAs alone (glycopeptides and aminoglycosides). Eight (6%) of these patients received two nephrotoxic antimicrobials.

The other 147 were treated intravenously with CMS, alone (CMS group, n = 90) or with one or more NAs (CMS + NAs group, n = 57). The NAs in the latter group were vancomycin in 39 cases, vancomycin plus amikacin in 7, amikacin in 5, gentamicin in 3, and vancomycin plus gentamicin in 3. In all cases, the infection was associated with at least one bacterial isolate that displayed persistent *in vitro* susceptibility to colistin only. In the subgroup that was also receiving NAs, patients also had one or more isolates displaying susceptibility to the specific NA being administered.

CMS was administered as Colimicina® (UCB Pharma SpA, Milan, Italy); 1 million UI per vial). All 147 patients received a loading dose of CMS (4 million IU) followed by a daily dose of 130,000 IU per kilogram of ideal body weight (IBW) (divided into three doses per day) [12]. For patients with creatinine clearance of less than 70 mL/min but more than 30 mL/min one-third of the normal daily dose twice a day (for example, 6 million IU divided into two doses per day for a 70 Kg patient); with a creatinine clearance <30 mL/min one-third of the normal daily dose once a day (for example, 3 million IU once a day for a 70 Kg patient); during CRRT we used one-third of the normal daily dose twice a day [13,14].

The median length of CMS therapy was 11 days; the cumulative CMS dose was 93.999.975 IU, and there were no significant differences between the CMS and CMS + NA subgroups involving any of these variables ($P = 0.26$ and $P = 0.37$, respectively)

Normogram based on creatinine clearance (CLCr) was used for calculation of the vancomycin daily dosage administered by continuous infusion in order to target a steady state concentration (CSS) at 15 to 20 mg/L [15]. We, therefore, confirm our dosage monitoring the serum vancomicin concentration. Aminoglycoside were administered according to one daily dosing schedule of 20 mg/kg/day for Amikacin and 5 mg/kg/day for Gentamycin; dosage was confirmed by monitoring the serum concentration and was adjusted as a function of CLCr. The target trough (1 μg/mL) was easily achieved using a once daily dose [16]

A total of 116 (41%) of the patients died while they were in ICU (Table 1).

One hundred eleven (40%) of the 279 patients developed AKI during their stay in the ICU. In the NAs group, 10% the AKI cases were classified as Risk, 13% as Injury and 18% as Failure; in the CMS group, 6% of the cases were classified as Risk, 7% as Injury and 22% as Failure; and in the CMS + NAs group, 7% of the AKI cases classified as Risk, 12% as Injury and 26% as Failure. The median onset of AKI was 10 days (8 to 15) (25^{th} to 75^{th}) in the CMS group, 11 days (10 to 12) (25^{th} to 75^{th}) in the NAs group, 12 days (10 to 21) (25^{th} to 75^{th}) in the CMS + NAs group. Compared with the non-AKI subgroup, those who developed AKI were significantly older and had significantly higher SAPS II scores. In addition, septic shock rates and ICU mortality were roughly three times higher than those in the non-AKI group; in fact, in the AKI group, the ICU mortality and septic shock rates were 70% and 74%, respectively (Table 2). The vast majority of AKI patients had an albumin serum level less than 2 g/dL (Table 2). The vast majority of the infections considered in this study were ventilator-associated pneumonia (VAP) or catheter-related bloodstream infections (CRBSIs), and in almost half of all cases (46%), septic shock was present at infection onset.

We did not find any difference in the incidence of AKI in respect to the etiology of infections among the

Table 1 ACEI, angiotensin converter enzyme inhibitor; AKI, acute kidney injury as defined per RIFLE criteria; BMI, body mass index; BSI, bloodstream infection; CMS, colistin methanesulfonate sodium; CRRT, continuous renal replacement therapy; CVC, central venous catheter; NSAID, nonsteroidal anti-inflammatory drug; Pts, patients; SAPS II, simplified acute physiology score two (calculated 24 h after ICU admission); VAP, ventilator-associated pneumonia.

VARIABLES	CMS (n = 90)	CMS + NAs (n = 57)	NAs (n = 132)
Age (years)	57 (40 to 69)	54 (39 to 66)	67 (48 to 76) *
Female, n (%)	32 (35)	20 (35)	40 (30)
SAPS II	41 (32 to 54)	44 (30 to 54)	44 (35 to 55)
BMI, Kg/m^2	25 (24 to 25)	24 (23.7 to 25)	24 (23 to 27)
ICU length of stay, (days)	28 (17 to 38)	33 (19 to 50)	15 (8 to 31) *
Albumin serum level <2 g/dL, n (%)	14 (15)	9 (16)	18 (14)
Total bilirubin serum level >5 mg/dL n (%)	7 (8)	4 (7)	11 (8)
NSAID n (%)	17 (19)	10 (18)	43 (33) ****
ACEI n (%)	15 (17)	3 (5)	16 (12)
i.v. iodate contrast n (%)	35 (39)	14 (25)	45 (34)
Immunocompromised pts n (%)	13 (14)	8 (14) ***	38 (29) * *
Reason for ICU admission			
Sepsis, n (%)	41 (46)	20 (35)	56 (43)
Neurological injury, n (%)	4 (4)	8 (14)	12 (9)
Traumatic injury, n (%)	31 (34)	21 (37)	31 (23)
Cardiovascular injury, n (%)	14 (16)	8 (14)	33 (25)
Comorbidity			
Hypertension, n (%)	14 (16)	12 (21)	28 (21)
Diabetes mellitus, n (%)	2 (2)	2 (3.5)	9 (7)
Congestive heart failure, n (%)	3 (3)	2 (3.5)	10 (7.5)
Two or more comorbidities, n (%)	5 (5)	4 (7)	16 (12)
Site of infection			
VAP, n (%)	69 (77)	40 (70)	91 (69)
CVC related-BSI, n (%)	18 (20)	13 (23)	31 (23)
Other, n (%)	3 [a] (3)	4[b] (7)	10 [c] (7)
Complications occurring during ICU stay			
CRRT, n (%)	13 (14)	14 (24)	29 (22)
AKI, n (%)	31 (34)	26 (45)	54 (41)
Septic shock, n (%)	31 (34)	27 (47)	70 (53)
ICU mortality, n (%)	31 (34)	21 (37)	64 (49)

Other nephrotoxic antimicrobial included aminoglycosides and glycopeptides.
[(a)] wound infection n = 2, abdominal abscess n = 1. [(b)] wound infection n = 1, abdominal abscess n = 1, urinary tract infection n = 2. [(c)] urinary infection n = 4, abdominal abscess n = 3, wound infection n = 1, meningitis n = 2. Values are given as the median (interquartile range).
* P <0.01 NAs *vs* CMS and CMS/NAs; ** P = 0.01 CMS vs NAs; *** P = 0.04 CMS/NAs vs NAs P = 0.03 ****

three groups studied. Nine out of 17 Failure patients who survived were discharged from ICU as Failure but without a dialysis prescription; 1 as Injury, 4 as Risk and 3 with a complete recovery of the renal function. Five out of 7 Injury patients who survived were discharged from ICU as Injury and 2 as Risk. Five out of 9 Risk patients who survived were discharged from ICU as Risk and 4 with a complete recovery of the renal function (Table 3).

The results of the logistic regression are shown in Tables 3, 4 and 5. In the complete study population (n = 279), the multivariate analysis showed that SAPS II scores and the presence of septic shock at infection onset were independently associated with AKI. The other significant variables at the univariate analysis were not included in the multivariate final logistic model using a stepwise procedure. A ROC curve analysis was performed to assess the accuracy of the final regression model showing AUC ± SE = 0.79 ± 0.03 with 95% C.I. 0.74 to 0.84; Chi Square statistics: P <0.001 (Table 4). In the 147 patients who received CMS (Table 5), the likelihood of developing AKI was not significantly different in the CMS and CMS + NA subgroups. In contrast, onset of AKI was two times more likely in patients with a SAPS II score ≥43 and six times more likely in those whose infections had presented with septic shock. A ROC curve

Table 2 ACEI, angiotensin converter enzyme inhibitor; AKI, acute kidney injury; BSI, bloodstream infection; CMS, colistin methanesulfate; CVC, central venous catheter; NAs, other nephrotoxic antibiotics (aminoglycosides, glycopeptides); NSAID, nonsteroidal anti-inflammatory drug; SAPS II, Simplified Acute Physiology Score Two (calculated 24 h after ICU admission); VAP, ventilator-associated pneumonia.

Variables	Total cohort (n = 79)	No AKI (n = 168)	AKI (n = 111)	*P*-value [a]
Age, years [b]	61 (43 to 74)	58 (39 to 71)	66 (51 to 77)	<0.01 *
Female, n (%)	92 (33)	62 (37)	30 (27)	0.09 **
SAPS II score [b]	44 (32 to 54)	38 (29 to 49)	50 (41 to 56)	<0.01 *
Septic shock at infection onset - n (%)	128 (46)	46 (27)	82 (74)	<0.01 **
Albumin serum levels <2 g/dL n (%)	38 (14)	15 (9)	23 (21)	<0.01 **
Total bilirubin serum levels >5 mg/dL n(%)	19 (7)	8 (5)	11 (10)	0.15 **
NSAID n (%)	70 (25)	48 (28)	22 (20)	0.13 **
ACEI n (%)	34 (12)	16 (10)	18 (16)	0.13 **
Immunocompromised pts n (%)	59 (21)	34 (20)	25 (23)	0.75 **
i.v. iodate contrast n (%)	94 (34)	53 (32)	41 (37)	0.42 **
Reason for ICU admission				
Sepsis, n (%)	117 (42)	60 (36)	57 (51)	0.01 **
Neurological disease, n (%)	24 (8)	18 (10)	6 (5)	0.18 **
Trauma, n (%)	83 (30)	62 (37)	21 (19)	<0.01 **
Cardiovascular disease, n (%)	55 (20)	28 (17)	27 (24)	0.15 **
Comorbidity				
Hypertension, n (%)	54 (20)	27 (16)	27 (24)	0.12**
Diabetes mellitus, (%)	13 (4)	6 (4)	7 (6)	0.44**
Congestive heart failure, n (%)	15 (6)	9 (5)	6 (5)	0.79 **
Two or more comorbidities	25 (9)	11 (6)	14 (13)	0.13 **
Type of infection				
VAP, n (%)	200 (72)	118 (70)	82 (74)	0.6 **
CVC related-BSI, n (%)	62 (23)	39 (23)	23 (21)	0.73 **
Other, n (%)	17 (5)	11 (7)[c]	6 (5) [d]	0.89 **
Treatment				
CMS, n (%)	90 (32)	59 (35)	31 (28)	0.25**
CMS+NAs, n (%)	57 (20)	31 (18)	26 (23)	0.39 **
CMS+ glycopeptides alone [e], n (%)	39 (68)	23 (59)	16 (41)	1***
CMS + aminoglicoside alone[e], n (%)	8 (14)	5 (62.5)	3 (37.5)	
NAs, n (%)	132 (47)	78 (47)	54 (48)	0.8 **
Outcome				
Days in ICU [b]	23 (13 to 37)	22 (13 to 34)	25 (14 to 42)	0.16 *
ICU mortality - n (%)	116 (41)	38 (23)	78 (70)	<0.01 **

[a] Differences between subgroups with and without AKI onset after ICU admission: *Mann-Whitney test; **Chi-squared test, *** Fisher's exact test

[b] Values are given as the median (interquartile range).

[c] wound infection n = 2, abdominal abscess n = 5, urinary tract infection n = 2, meningitis n = 2

[d] wound infection n = 1, abdominal abscess n = 3, urinary tract infection n = 2

[e] in this analysis were excluded the patients who received aminoglycoside + glycopeptide (n = 10) (18%)

Table 3 Outcome at the ICU discharge of AKI patients

AKI during ICU stay	Outcome at ICU discharge				
	Normal (n)	Risk (n)	Injury (n)	Failure (n)	Dead (n)
Risk n = 22	4	5	0	0	12
Injury n = 30	0	2	5	0	21
Failure n = 59	3	4	1	9	45

analysis was performed to assess the accuracy of the final regression model showing AUC ± SE = 0.76 ± 0.04 with 95% CI 0.7 to 0.8; Chi-square statistics P <0.001.

A similar picture emerged when we analyzed the 222 patients who received CMS alone (n = 90) or NAs alone (n = 132) (Table 6). The only independent predictors of AKI in this group were SAPS II scores ≥44 and septic shock at infection onset. A ROC curve analysis was

Table 4 Logistic regression analysis of factor associated with AKI in the study cohort

	Univariate analysis			Multivariate analysis		
Variables	**O.R.**	**95% C.I.**	***P*-value**	**O.R.**	**95% C.I.**	***P*-value**
Age, years	1.02	1.01 to 1.04	<0.01			
SAPS II score	1.04	1.03 to 1.06	<0.01	1.03	1.01 to 1.05	<0.01
Female	0.63	0.37 to 1.06	0.08	0.62	0.34 to 1.14	0.12
Septic shock at infection onset	7.5	4.36 to 12.9	<0.01	5.89	3.35 to 10.35	<0.01
Albumin serum levels <2 g/dL	2.66	1.32 to 5.37	<0.01			
Total bilirubin serum levels >5 mg/dL	2.2	0.85 to 5.65	0.1			
NSAID	0.62	0.35 to 1.1	0.1			
ACEI	1.83	0.89 to 3.78	0.1			
i.v. iodate contrast	1.27	0.76 to 2.1	0.35			
Immunocompromised status	1.14	0.63 to 2.05	0.64			
Causes of ICU admission						
Sepsis	1.9	1.17 to 3.1	<0.01	1.74	0.99 - 3.05	0.052
Neurological disease	0.47	0.18 to 1.24	0.13			
Trauma	0.4	0.22 to 0.7	<0.01			
Cardiovascular disease	1.61	0.89 to 2.9	0.12			
Co-morbidities						
Hypertension	1.68	0.92 to 3.05	0.09			
Diabetes mellitus	1.79	0.58 to 5.47	0.31			
Congestive heart failure	1	0.35 to 2.92	0.99			
Two or more comorbidities	2.06	0.9 to 4.72	0.08			
Type of infection						
VAP	1.19	0.7 to 2.05	0.51			
CVC related-BSI	0.86	0.48 to 1.55	0.62			
Other	0.81	0.29 to 2.27	0.7			
Treatment with CMS (vs. NAs)	0.91	0.56 to 1.47	0.7			

The variables included in the final predictive model were selected with a stepwise procedure: albumin serum levels <2 g/dL, total bilirubin serum levels >5 mg/dL, ACE inhibitors, NSAID, age, neurological disease, trauma, cardiovascular disease, hypertension and two or more co-morbidities were variables not included in the final model. We assessed discrimination of the model with area under the receiver operating curve (AUC ± SE = 0.79 ± 0.03 with 95% C.I. 0.74 to 0.84; Chi Square statistics: P <0.001).

ACEI, angiotensin converter enzyme inhibitor; AUC, area under the curve; BSI, bloodstream infection; CI, confidence interval; CMS, colistin methanesulfate; CVC, central venous catheter; NAs, other nephrotoxic antibiotics (aminoglycosides, glycopeptides); NSAID, nonsteroidal anti-inflammatory drug; SAPS II, Simplified Acute Physiology Score Two (calculated 24 h after ICU admission); VAP, ventilator-associated pneumonia.

performed to assess the accuracy of the final regression model showing AUC = 0.8 ± 0.03 with 0.75 to 0.86 95% CI; Chi-square statistics: P <0.01.

These findings indicate that in ICU patients without pre-existing renal disease who require nephrotoxic antimicrobial drug therapy for XDR bacterial infections, the use of CMS - with or without NAs - does not significantly increase the risk for AKI over that associated with NAs therapy alone.

Discussion

The cohort treated with high doses of CMS for nosocomial XDR infections in our study represented approximately 10% of the entire population admitted to the general ICUs during the two-year study period. The overall incidence of AKI in the 279 cases we analyzed was 40%, and there were no significant differences among rates observed in the CMS (34%), CMS+NAs (45%) and NAs subgroups (41%). These data are consistent with the results of the Nefroint study [8], a multicenter study conducted in Italian ICUs: in the subgroup of 133 patients without AKI at ICU admission, the incidence of AKI was 40% regardless of whether or not nephrotoxic drugs were administered. A recent meta-analysis [17] on six controlled studies comparing colistin vs other antibiotics for treatment of VAP in patients without cystic fibrosis suggested that colistin may be as safe as other standard antibiotics used for these drug-resistant infections. In particular, the nephrotoxicity rate for colistin was similar to that in the control group.

Our multivariate analysis revealed that SAPS II scores ≥43 and the presence of septic shock at infection onset were independently associated with AKI, but high-dose intravenous CMS therapy for more than seven days was not a risk factor for development of new onset AKI.

Since CMS's recent re-emergence as a last-resort treatment of infections caused by XDR pathogens

Table 5 Logistic regression analysis of factors associated with AKI in patients who received CMS and CMS/NAs.

		Univariate analysis			Multivariate analysis[b]		
Variables	**No. AKI/total (%)**	**O.R.**	**95% C.I.**	***P*-value**	**O.R.**	**95% C.I.**	***P*-value**
Age, years [a]							
<55	23/71 (32)	1.00					
≥55	34/76 (45)	1.68	0.86-3.31	0.13			
Sex							
Male	39/95 (41)	1.00					
Female	18/52 (34)	0.76	0.37-1.53	0.44			
SAPS II [a]							
<43	20/73 (27)	1.00					
≥43	37/74 (50)	2.65	1.33-5.27	<0.01	2.26	1.07-4.79	0.03
Septic shock at Infection onset							
No	20/89 (22)	1.00					
Yes	37/58 (64)	6.1	2.92-12.62	<0.01	5.64	2.66-11.94	<0.01
Treatment with CMS							
CMS with NAs	26/57 (45)	1.00					
CMS alone	31/90 (34)	0.62	0.31-1.23	0.17			
Cumulative CMS dose [a,c]							
<93.999.975 (IU)	33/73 (45)	1.00					
≥93.999.975 (IU)	24/74 (32)	0.58	0.29-1.13	0.11	0.61	0.29-1.29	0.19
Duration of CMS therapy[a]							
<11 days	30/72 (42)	1.00					
≥11 days	27/35 (36)	0.78	0.4-1.53	0.48			

The variables included in the final predictive model were selected with a stepwise procedure: age and treatment with CMS were not included in the final model.
[a] age, SAPS II, duration of CMS therapy, and cumulative CMS dose were dichotomized around median values. [b] The ROC curve analysis was used to assess the goodness of the final logistic regression model (AUC ± SE = 0.76 ± 0.04 with 95% CI 0.7 to 0.8; Chi-square statistics *P* <0.001). [c] Includes loading dose of 4,000,000 IU.
AKI, acute kidney injury; AUC, area under the curve; CI, confidence interval; CMS, colistin methanesulfate; IBW, ideal body weight; IU, international unit; NAs, nephrotoxic antibiotics (aminoglycosides, glycopeptides); ROC, receiver operating characteristic; SAPS II, Simplified Acute Physiology Score II (calculated 24 h after ICU admission).

Table 6 Logistic regression analysis of factors associated with AKI in patients who received CMS and NAs

		Univariate analysis			Multivariate analysis[b]		
Variables	**No. AKI/total (%)**	**O.R.**	**95% C.I.**	***P*-value**	**O.R.**	**95% C.I.**	***P*-value**
Age, years [a]							
<64	36/110 (32)	1.00					
≥64	49/112 (43)	1.59	0.92-2.75	0.09			
Sex							
Male	63/150 (42)	1.00					
Female	22/72 (30)	0.6	0.33-1.1	0.1	0.6	0.29-1.2	0.15
SAPS II [a]							
<44	25/109 (22)	1.00					
≥44	60/113 (53)	3.8	2.13-6.79	<0.01	2.45	1.17-4.74	<0.01
Septic shock at Infection onset							
No	19/121 (15)	1.00					
Yes	66/101 (65)	10.12	5.34-19.12	<0.01	8.24	4.26-15.93	<0.01
Treatment with CMS							
No	54/132 (41)	1.00					
Yes	31/90 (34)	0.75	0.43-1.32	0.33			

The variables included in the final predictive model were selected with a stepwise procedure: age was not included in the final model.
[a] Age, SAPS II were dichotomized around median values.
[b]The ROC curve analysis was used to assess the goodness of the final logistic regression model (AUC = 0.8 ± 0.03 with 0.75 to 0.86 95% CI; Chi-square statistics: *P* <0.01)
AKI, acute kidney injury; AUC, area under the curve; CI, confidence interval; CMS, colistin methanesulfate; NAs, nephrotoxic antibiotics (aminoglycosides, glycopeptides); ROC, receiver operating characteristic; SAPS II, Simplified Acute Physiology Score Two (calculated 24 h after ICU admission).

(including *Acinetobacter baumanii, Pseudomonas aeruginosa* and *Klebsiella pneumonia*), many authors have investigated its adverse effects, in particular, its potential nephrotoxicity. Like aminoglycosides, the polymyxins cause damage to the kidneys at the level of the proximal tubules, where both classes of drugs are extensively reabsorbed via the endocytic receptor protein megalin [18]. Colistin was originally used in the 1960s to combat infections caused by gram-negative bacteria, but it was abandoned in the 1970s because of its reported association with high nephrotoxicity rates [13,19] and because new, apparently less toxic antibiotics (for example, the aminoglycosides) were becoming available. Several studies published over the past decade, however, have demonstrated that CMS is not associated with serious adverse effects, and although nephrotoxicity incidence rates varied (0% to 32%) [20-24], they were clearly lower than those reported in the 1960s and 1970s. The differences between older and more recent findings have been attributed to various factors, including the increased presence of chemical impurities in older colistin preparations, the variable definitions of acute renal impairment used in the various studies, closer monitoring and, last but not least, the improved maintenance of patient hydration by today's physicians [20].

Research endorsed by the Acute Dialysis Quality Initiative led to the publication of the RIFLE classification, with standardized criteria for various degrees of renal dysfunction [6]. The RIFLE approach can detect AKI with high sensitivity and high specificity. It can also be used to predict the prognosis of affected patients, and it provides a useful framework for comparing the results of different studies. Two recent studies that used the RIFLE criteria to investigate colistin-related nephrotoxicity [25,26] documented high incidences of mild renal impairment (about 43%) in both cohorts (even though the two populations differed in terms of illness severity).

Indeed, in most recent studies, the colistin-treated populations have been heterogeneous in terms of baseline illness severity, baseline renal function and treatment variables, including daily doses and duration of treatment. Daily doses of CMS used in these studies ranged from 3 million to 11 million IU [21,25,27-30]. To make matters worse, there is also wide variation involving the type of preparation used, that is, CMS (where 2 million IUs correspond to 160 mg of the drug) versus colistin base (where 2 million IUs equals 60 mg). The importance of universal dosing terminology has been emphasized by several investigators [19,20].

This antibiotic is being used with increasing frequency to treat critically ill patients - despite the absence of clinical guidelines and dosing recommendations for this particular population. Multi-organ dysfunction and severe XDR infections can alter the pharmacokinetics of CMS and colistin in terms of half-life and rates of formation of colistin from CMS [30], and the larger volumes of distribution present in these critically ill septic patients can cause a lower concentration of the antibiotic [5]. Early and appropriate goal-directed fluid therapy is fundamental in acute resuscitation of these critically ill patients; however, it is almost always associated with a certain degree of fluid overload, especially in septic patients, which promotes tissue edema that could potentially contribute, itself, to progressive organ dysfunction. Both fluid balance and urine volume are independent predictors of mortality in adult critically ill patients with AKI [31].

Plachouras *et al*. [12] studied the pharmacokinetics of intravenously administered CMS in critically ill patients and concluded that a loading dose of at least 9 million IU of CMS is needed in these cases to produce plasma concentrations of the drug within the minimum inhibitory concentration (MIC) range indicative of susceptibility. Failure to achieve such concentrations can lead to the emergence of resistant strains, and it can also result in increased mortality.

In light of these findings, we decided to investigate the nephrotoxicity of high-dose CMS therapy, in terms of RIFLE-defined AKI, in patients with no AKI at baseline. Hartzell and collaborators [25] used a similar approach in a young and otherwise healthy population of patients on a general medicine ward. The patients had no other confounding comorbidity, but the mean duration of CMS therapy was longer than it was in our study. The authors found a significant association between the cumulative CMS dose and the risk of nephrotoxicity in patients receiving CMS for more than 14 days. This finding contrasts with the results of our logistic regression analysis, which showed that neither the cumulative CMS dose nor the duration of treatment was a risk factor for developing new-onset AKI in severely ill ICU patients. The median days of CMS treatment of our patients, however, was lower that than reported by Hartzell and collaborators and could probably justify the discordance with our results as well as the difference in severity of the two population studied. We agree, nevertheless, that creatinine levels need to be closely monitored in patients receiving prolonged treatment with CMS.

Pogue *et al*. [26] reported that CMS nephrotoxicity is related to the daily dose but not to cumulative exposure. However, the population they studied was heterogeneous in terms of pre-treatment renal function. Furthermore, although illness severity scores were not reported, their patients were probably not as critically ill as ours. Only 14% had septic shock, 15% were on vasopressors and only 62% were being mechanically ventilated. These

are important differences because, as noted above, the pharmacokinetics of CMS and colistin are different in the critically ill [5,29], and in our study a SAPS II score ≥43 was independently associated with AKI. Comparison of findings in ICU and non-ICU cohorts is also complicated by the fact that the former patients are likely to be more closely monitored and more rapidly treated than those being cared for on general wards.

Septic shock was the strongest predictor of AKI in our cohort. Many authors agree that the renal effects of sepsis, *per se*, should not be underestimated. Early AKI is common in septic shock [32], and it may potentiate the effects of colistin and other drugs on the kidney. The combination of septic shock and AKI had a consistently negative effect on survival. Among the patients with septic shock who did not receive CMS at all (that is, those who were treated with NAs alone), the incidence of AKI was 64% (45/70), which confirms the predominant role of septic shock in the kidney injury (Figure 1).

Limitation of the study

The main limitation of our study is its retrospective design. This shortcoming is partially compensated for by the large number of patients studied, but it is almost impossible to avoid. A prospective randomized trial would inevitably be associated with ethical problems since for many infections, colistin is the only treatment option.

None of the patients received the CMS as empirical therapy and a definitive appropriate therapy was achieved within 36/48 hours. There are no data showing that using CMS as an empiric regimen could reduce the risk of inappropriate therapy and/or could reduce the incidence of septic shock or increase the risk of AKI. These interesting issues should be tested by specific trials.

Conclusions

In conclusion, in ICU patients with normal baseline renal function who receive CMS and/or NAs, the incidence of AKI as defined by the RIFLE classification is clearly high - 40%. However, high-dose CMS therapy does not appear to be a risk factor for this outcome. Instead, the development of AKI was strongly correlated with the presence of septic shock and with the severity of the patients' underlying illness, as reflected by the SAPS II score. These findings suggest that renal protection measures, such as blood volume maintenance, are of utmost importance in critically ill patients with infections that require treatment with CMS.

Key messages

- The incidence of AKI in critically ill patients without pre-existing renal diseases is strongly correlated with the presence of septic shock and with illness severity.
- Compared with other nephrotoxic antimicrobials, high-dose CMS does not appear to increase the risk of new-onset AKI in this setting.

Abbreviations

ACEI: angiotensin converter enzyme inhibitor; ADQI: Acute Dialysis Quality Initiative; AKI: acute kidney injury; BSI: bloodstream infection; CMS: colistin methanesulfonate; ClCr: creatinine clearance; CRBSIs: catheter-related bloodstream infections; CRRT: continuous renal replacement therapy; CSS: steady state concentration; IBW: ideal body weight; ICU: intensive care unit; IQR: interquartile ranges; IU: international units; i.v.: intravenous; GFR: glomerular filtration rate; MDRD: Modification of Diet in the Renal Disease; MIC: minimum inhibitory concentration; NAs: nephrotoxic antimicrobials; NSAID: nonsteroidal anti-inflammation drug; ORs: odds ratios; RIFLE: Risk Injury-Failure-Loss-End-stage kidney disease; ROC: receiver operating characteristic; SAPS II: Simplified Acute Physiology Score II; Scr: serum creatinine; VAP: ventilator associated pneumonia; XDR: extensively drug-resistant

Competing interests

The authors have no competing interests to declare relative to this article.

Authors' contributions

MR, LM, EA, MV, PP and MA designed the study. AL, MV, GR and GDP collected and assembled the data. LM and EA performed the statistical analysis. MR, LM, MA, EA, PP and AL drafted the manuscript, and all authors have read and approved the final manuscript.

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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection

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Abstract
Purpose Colistin, which had not been used widely because of nephrotoxicity and neurotoxicity, has gained clinical importance in recent times due to the resurgence of multidrug-resistant Gram-negative bacilli. Very few studies, especially pharmacokinetic studies, have been performed with intravenous colistimethate sodium, and none in India. The aim of our study was to study the single-dose and steady-state pharmacokinetics of colistin in patients with multidrug-resistant Gram-negative bacilli infections.
Method This was a prospective open-label pharmacokinetic study done in an intensive care unit in a tertiary care hospital on 15 critically ill patients with proven multidrug-resistant Gram-negative bacilli infection. Colistimethate sodium was injected as intermittent intravenous infusions in accordance with the recommendations on the package insert. For patients weighing ≥60 kg with a normal renal function or with a creatinine clearance (CL_{CR}) of between 20 and 50 ml/min, the drug was administered at 2 million international units (MIU) every 8 h; for those with a CL_{CR} of 10–20 ml/min, the dose was 2 MIU every 12 h. Those patients who weighed <60 kg were administered 50,000 IU/kg/day in three divided doses at 8-h intervals. Both single-dose and steady-state pharmacokinetics of colistin were determined and correlated with clinical outcomes.
Results A wide inter-individual variation was observed in pharmacokinetic parameters. The median (range) of the maximum plasma drug concentration/minimum inhibitory concentration (C_{max}/MIC) ratio for *Acinetobacter* spp. was 13.4 (1.3–40.3) following the administration of a single dose of colistimethate sodium and 26.3 (0.9–64.9) at steady-state. For *Pseudomonas* spp., these values were 3.18 (1.6–23.1) following the single dose and 3.82 (2.3–10.9) at steady-state. For those patients whose cultures grew *Acinetobacter* spp., an optimum value of the C_{max}/MIC ratio of >8 was achieved in seven of nine patients after the single dose and in seven of eight patients at steady-state. For those patients whose cultures grew *Pseudomonas* spp, only one patient after the single dose and one patient at steady-state achieved a C_{max}/MIC ratio of >8. A significant association was noted between dose and survival, and a trend was observed with patients weighing ≤60 kg (who received 50,000 IU/kg/day instead of 6 MIU/day for those >60 kg) having an increased mortality.
Conclusion The pharmacokinetic parameters of colistin were comparable to those reported in previous studies in critically ill patients. However, the recommended dose may be inadequate to maintain the C_{max}/MIC ratio to an optimal level—at least in patients infected with *Pseudomonas* spp. The dose recommendation should be based only on creatinine clearance and not body weight.

Keywords Multidrug-resistant Gram-negative bacilli · Colistimethate sodium · Single dose · Steady-state · Pharmacokinetics

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Introduction

The escalating incidence of infections due to multidrug resistant (MDR) Gram-negative bacilli, particularly among critically ill patients, is a worldwide problem and is associated with significant morbidity and mortality [1–3]. In the search for effective antimicrobials, there has been an increased interest in an old antibiotic, colistin [4–7]. Although introduced in 1959, the drug has not been widely used because of its association with a high incidence of nephrotoxicity and neurotoxicity [8].

Colistin is a cationic, multicomponent (including colistin A and B) lipopeptide antibiotic that is intravenously administered as its prodrug, colistimethate sodium [9]. The drug exhibits concentration-dependent bactericidal activity against *Acinetobacter baumannii* [10] and *Pseudomonas aeruginosa* [11], and several studies have shown its efficacy in the treatment of the infections caused by these microorganisms [12–14]. The European Committee on Antimicrobial Susceptibility Testing has specified a minimum inhibitory concentration (MIC) of≤2 mg/l for these microorganisms to be called susceptible [15].

There is a dearth of pharmacological information on colistin, possibly because it did not undergo rigorous drug development studies prior to marketing as is required today. The recent interest in colistin has highlighted the lack of adequate pharmacokinetic and pharmacodynamic data to guide dosing [7, 16]. Very few studies have been conducted to evaluate the pharmacokinetics of colistin following intravenous colistimethate sodium worldwide [17–21], and none have been conducted in India. Therefore, the aim of our study was to assess the single-dose as well as steady-state pharmacokinetics of the colistin base in critically ill patients with MDR Gram-negative infections in a tertiary care hospital in India.

Patients and methods

This was a prospective, non-comparative, open label study conducted between September 2009 and August 2010. Institutional Review Board (IRB) approval was obtained, and the study was registered with Clinical Trial Registry of India (CTRI/2009/091/000252).

Patients

Critically ill patients (14 adults, 1 adolescent) admitted to the medical intensive care unit with bacteriologically documented MDR Gram-negative infections were enrolled in the study after written informed consent had been obtained from the patients or their legally accepted representatives. MDR infections due to Gram-negative bacilli were defined as resistance to three or more of the antimicrobials, including penicillins, cephalosporins, betalactams + beta lactamase inhibitors, fluoroquinolones, carbapenems, but sensitivity to colistin as per microbiological culture report [22]. Detailed history and physical examination findings were noted daily, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and findings from chest X-ray, 12-lead electrocardiogram and routine hematological and biochemical investigations were recorded at baseline. The baseline creatinine clearance (CL_{CR}) (estimated by Cockcroft–Gault formula [23]) guided the calculation of dose, and the measurement was repeated daily. A urine pregnancy test was performed in women of child bearing age before the administration of colistimethate sodium. Blood and bronchoalveolar lavage specimens were obtained prior to drug administration and processed for Gram stain and culture, antibiotic sensitivity and a measurement of the MIC for colistin. Patients with a CL_{CR} of <10 ml/min, aged <18 years (one adolescent of age 15 years was included after obtaining permission from the IRB) or >65 years and/or diagnosed as myasthenia gravis were excluded; pregnant and breastfeeding women were also excluded.

The patients were administered the drug as described below for a duration ranging from a minimum of 8 to a maximum of 14 days depending on clinical need. Only those patients who received the drug for at least 8 days were considered to have completed the study. If the patients' CL_{CR} fell to <10 ml/min during the treatment, they were withdrawn from the study.

Outcomes

Clinical outcomes Clinical cure was defined when the complete resolution of clinical findings (signs and symptoms, leukocytosis and chest X-ray) were noted. If there was partial resolution, it was considered as clinical improvement. Clinical failure was defined as the persistence or worsening of symptoms and/or signs of infection at 72 h after starting colistimethate sodium.

Bacteriological outcomes The outcome was labeled eradication when there was no growth of the pathogen in the final culture (last day of colistimethate sodium injection), and persistence if the growth was seen regardless of clinical outcome. When microbiological assessment was not possible, it was considered as undetermined.

Safety outcomes The safety parameters that were included in the study were mortality, adverse events and any clinically significant changes in the laboratory values.

Methods

Drug administration All patients received colistimethate sodium (Xylistin™; Batch number XP-9001; Cipla Ltd.,

Mumbai Central, Mumbai, India) administered intravenously over 30 min at a dose calculated according to the recommendations on the product's label. For patients weighing ≥60 kg with normal renal function or with a CL_{CR} between 20 and 50 ml/min, the drug was administered at 2 million international units (MIU) every 8 h; for those with a CL_{CR} of 10–20 ml/min, 2 MIU was administered every 12 h. Patients weighing <60 kg were administered 50,000 IU/kg/day in three divided doses at 8-h intervals. The powder was dissolved in 50 ml normal saline for infusion.

Blood sampling Blood samples (3 ml in a plain test tube) were collected on day 1 (single dose) and day 4 (steady-state) following the initiation of colistimethate sodium injections, prior to dose administration and at 30 and 40 min and 1, 2, 4, 6 and 8 h post-drug administration. Pre-dose samples were also collected on days 2, 3, 5, 6 and 7. The serum was separated and stored at −70 °C pending analysis.

Drug estimation by liquid chromatography–tandem mass spectrometry A bioanalytical method for the simultaneous assay of both colistin A and colistin B from serum samples was developed and validated based on an earlier method described by Zheng Ma et al. [24]. Analytes (colistin A and B) were extracted from serum samples by protein precipitation followed by solid phase extraction. Quantitation was performed using the liquid chromatography–tandem mass spectrometry instrument API 4000 (Applied Biosystems, Foster City, CA) by multiple reaction monitoring transitions as 585.60 → 101.20 and 578.60 → 227.60 for colistin A and colistin B, respectively. Polymyxin B was used as an internal standard. The chromatographic method involved the use of volatile ion pairing reagent heptaflurobutyric acid as mobile phase additive and a C18 analytical column. The use of an ion pairing reagent helped in achieving good sensitivity, resolution of analytes from endogenous matrix and good peak shapes. The drug concentration curve was linear in serum samples between 9.6 and 1434.5 ng/ml for colistin A and between 30.0 and 4493.8 ng/ml for colistin B. The matrix effect was evaluated using the results from post-column infusion and post-extraction addition experiments. This method was validated for specificity, selectivity, sensitivity, precision and accuracy, stability (stock solution, post-preparative, short term, freeze-thaw and long term), recovery, dilution integrity, re-injection reproducibility and ruggedness. The precision for colistin A and colistin B ranged between 2.28 and 9.05 % and between 2.82 and 6.34 %, respectively. The accuracy for colistin A and colistin B ranged between 93.75 and 105.23 % and between 96.53 and 106.91 %, respectively.

Statistical analysis

No formal sample size calculations were performed. The pharmacokinetic analysis was performed using WinNonLin ver. 5.3; Pharsight, St. Louis, MO). In each participant, age, weight, APACHE II score, colistin dose, CL_{CR} and all pharmacokinetic parameters were considered as quantitative continuous variables and expressed as the median (range). All significant associations were represented with the 95 % confidence interval (CI). Sex and survival were considered as categorical variables. The normality of the data was checked by using the Kolmogorov–Smirnov test.

Post hoc analysis

Although the study was primarily envisaged as a pharmacokinetic study, as the study was progressing, we observed certain differences in the clinical outcomes between patients who had received the drug at different doses. Also, there is a paucity of data on survival with colistin. Hence, a number of post hoc tests were carried out. The Spearman rank correlation coefficient was calculated using single-dose and steady-state maximum plasma drug concentration (C_{max}) as dependant variables and age, APACHE II score, CL_{CR} and dose of colistimethate sodium as independent variables. To assess the correlation between the single-dose and steady-state C_{max}/MIC ratio, the Spearman rank correlation test was used with the APACHE II score and dose of colistimethate sodium as independent variables. A binary logistic regression analysis was carried out between various predictor variables (age, body weight, APACHE II scores, CL_{CR}, dosage, single-dose and steady-state C_{max}) and survival using Minitab ver. 16.0 statistical software (2010; Minitab Inc., State College, PA: www.minitab.com), and correlation between the predictor variables with single-dose and steady-state C_{max} and single-dose and steady-state C_{max}/MIC ratio was performed using the Spearman rank correlation coefficient with GraphPad Instat ver. 3.05 for Windows 95 (GraphPad Software, San Diego CA: www.graphpad.com). A p value of <5 % was considered to be significant.

Results

Demographic data

Of the 15 patients enrolled, eight were men and seven were women. The median (range) APACHE II score was 9 (4–16) and median (range) CL_{CR} was 125 (49.16–220.8) ml/min. The indication for administering colistimethate sodium was ventilator-associated pneumonia in all of the study patients. Demographic details of the individual study patients are described in Table 1. Of the 15 patients, four died before

Table 1 Demographic details

Patient number	Sex	Age (years)	Body weight (kg)	Dose (MIU) per day	Diagnosis	CL_{CR} (ml/min)	APACHE II scoring	Outcome	Specimen	Bacteriological profile
1.	M	22	60	6	Guillain-Barre syndrome	49.16	13	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii*
2.	F	30	65	6	Polymyositis	167.28	6	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
3.	F	15	50	2.5	Viral encephalitis	81.94	5	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
4.	M	22	65	6	Guillain-Barre syndrome	133.8	5	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
5.	F	27	50	2.5	Acute respiratory distress syndrome/ Pulmonary tuberculosis	84	16	Died	Blood	*Klebsiella pneumoniae* and *Pseudomonas spp.*
6.	F	21	55	2.75	Organophosphorus poisoning	99.89	11	Died	Bronchoalveolar lavage	*Acinetobacter spp.*
7.	F	37	55	2.75	Organophosphorus poisoning	70.39	9	Died	Bronchoalveolar lavage	*Pseudomonas spp.*
8.	M	35	60	6	Acute respiratory distress syndrome	105.4	6	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
9.	M	20	62	6	Tetanus	172.22	10	Survived	Blood	*Pseudomonas aeroginosa*
10.	M	19	62	6	Guillain-Barre syndrome	173.65	4	Survived	Bronchoalveolar lavage	*Acinetobacter baumanii* and *Pseudomonas spp.*
11.	M	37	68	6	Nephrotic syndrome	154.4	14	Died after study completion	Bronchoalveolar lavage	*Acinetobacter spp.*
12.	F	27	60	6	Frontal arteriovenous malformation	125	11	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
13.	M	40	60	6	Guillain-Barre syndrome	88.65	6	Survived	Bronchoalveolar lavage	*Acinetobacter spp.*
14.	F	22	65	6	Guillain-Barre syndrome	220.8	8	Survived	Bronchoalveolar lavage	*Acinetobacter spp.* and *Methicillin Resistant Staphylococcus aureus*
15.	M	35	85	6	Cerebrovenous accident	126.48	14	Died	Bronchoalveolar lavage	*Acinetobacter spp.*

MIU, Million international units; CL_{CR}, creatinine clearance, APACHE, Acute Physiology and Chronic Health Evaluation II Score; M, male; F, female

completing the study, seven showed clinical cure and four showed clinical improvement. Of the latter, one patient died due to progression of the underlying pathology.

Bacteriological profile and outcome

The bacteriological profile is shown in Table 1. A total of 13 samples showed resistance to imipenem. The MICs for these organisms were available for 12 patients and the median (range) were 0.38 (0.25–2) and 1.5 (1–2) μg/ml for *Acinetobacter* spp. and *Pseudomonas* spp., respectively. The details of bacteriological and other outcomes are given in Table 2.

Dose of colistimethate sodium

Of the 15 patients, 11 received 2 MIU colistimethate sodium at 8-h intervals while four received 50,000 IU/kg/day in three divided doses calculated on the basis of body weight and CL_{CR}. The median (range) dose of colistimethate sodium was 6 (2.5–6) MIU per day.

Pharmacokinetic parameters

Single-dose pharmacokinetic data were available for 13 patients (data could not be obtained in 2 patients due to analytical problems), and both the single-dose and steady-state pharmacokinetic data were available for 11 patients (2 of 13 patients died within day 4 of colistin treatment initiation).

A wide inter-individual variability was seen in the pharmacokinetic parameters. The median (range) C_{max}, elimination half life ($t_{½}$) and clearance (CL) were 4.6 (2.5–23.2) μg/ml, 2.7 (1.1–4.6) h and 1.3 (1.0–2.1) ml/min/kg, respectively, after a single dose, and 5.4 (1.8–21.8) μg/ml, 3.3 (1.2–5.4) h and 1.1 (0.7–1.9) ml/min/kg, respectively, at steady-state (after day 4 dose). The summary of the various pharmacokinetic parameters is depicted in Table 3, and mean concentrations following the single dose and at steady-state at various time points are shown in Figs. 1 and 2, respectively.

The median (range) C_{max}/MIC ratio following a single dose and at steady-state was 13.4 (1.3–40.3) and 26.3 (0.9–64.9), respectively, for *Acinetobacter* spp. and 3.2 (1.6–23.1) and 3.8 (2.3–10.9), respectively, for *Pseudomonas* spp..

Other analyses

Binary logistic regression showed a significant association of survival with the dosage of the drug (p=0.046). Three of the four patients weighing≤60 kg (received 50,000 IU/kg/day) died and two of the 11 weighing>60 kg (received 2 M IU at 8-h intervals) died (Fisher exact probability test p=0.077). The dose of colistimethate sodium was significantly correlated with C_{max} (single-dose: ρ=0.65, 95 % CI 0.14–0.89, p=0.02; steady-state: ρ=0.78, 95 % CI 0.33–0.94, p=0.01) and C_{max}/MIC ratio (single-dose: ρ=0.57, 95 % CI 0.01–0.85, p=0.04; steady-state: ρ=0.65, 95 % CI 0.09–0.89, p=0.02). A significant correlation was also found between steady-state C_{max} and body weight (ρ=0.66, 95 % CI 0.07–0.90, p=0.03).

Adverse events

Adverse events noted in the study participants are mentioned in Table 2. Amongst those with elevated liver enzymes, only one had a possible causal relation to the drug. Hyponatremia, hypokalemia and convulsion were seen in one participant (possibly related) and a serious adverse

Table 2 Bacteriological, clinical and safety outcomes

Patient number	Bacteriological outcome	Clinical outcome	Safety outcome
1.	Growth persisted but sensitive to colistin	Clinical improvement	Elevated liver enzymes
2.	Growth persisted but sensitive to colistin	Clinical cure	Elevated liver enzymes
3.	Growth persisted but sensitive to colistin	Clinical improvement	Hyponatremia, hypokalemia, convulsion
4.	Eradication of pathogen	Clinical cure	Elevated liver enzymes
5.	Bacteriological response could not be performed	Clinical failure	Death
6.	Bacteriological response could not be performed	Clinical failure	Death
7.	Bacteriological response could not be performed	Clinical failure	Elevated liver enzymes, death
8.	Eradication of pathogens	Clinical cure	None
9.	Growth persisted but sensitive to colistin	Clinical improvement	Leg pain
10.	Eradication of pathogens	Clinical cure	None
11.	Eradication of pathogens	Clinical cure	None
12.	Growth persisted but sensitive to colistin	Clinical improvement	Death
13.	Growth persisted but sensitive to colistin	Clinical cure	None
14.	Bacteriological response could not be performed	Clinical failure	Death
15.	Growth persisted but sensitive to colistin	Clinical improvement	None

event in the form of death due to septicemia was reported in five patients (causality: unlikely). No other major adverse events were noted.

Concomitant medications

Broadly, the drug classes that were administered concomitantly included other antimicrobials, corticosteroids, biologicals, anti-coagulants, anticonvulsants, intravenous fluids and cardiac inotropes. None of these are known to interact with colistimethate sodium pharmacokinetically.

Discussion

Our study is the first to be carried out in India that documents the single-dose and steady-state pharmacokinetics of colistin in critically ill patients. The pharmacokinetic parameters showed wide inter-individual variability, and the single-dose and steady-state pharmacokinetic parameters did not differ significantly. The steady-state parameters were similar to those reported in critically ill Caucasian patients [18, 20], and the overall survival rate of 66.67 % was also comparable to that reported in other studies [25, 26].

Table 3 Summary of the single-dose and steady-state pharmacokinetic data

Pharmacokinetic parameter	Single-dose PK value[a]	Steady-state PK value[a]
C_{max} (μg/ml)	4.6 (2.5–23.2)	5.4 (1.8–21.8)
AUC_8 (mg.hr/l)	11.2 (5.4–16.4)	15.7 (5.0–26.7)
AUC_∞ (mg.hr/l)	12.9 (5.6–18.9)	19.7 (5.2–41.8)
$t_{1/2}$ (h)	2.7 (1.1–4.6)	3.3 (1.2–5.4)
V_d (l/kg)	0.3 (0.2–0.5)	0.3 (0.2–0.5)
CL (ml/min/kg)	1.3 (1.0–2.1)	1.1 (0.7–1.9)
C_{max}/MIC (*Acinetobacter* spp.)	13.4 (1.3–40.3)	26.3 (0.9–64.9)
C_{max}/MIC (*Pseudomonas* spp.)	3.2 (1.6–23.1)	3.8 (2.3–10.9)
AUC_∞/MIC (h) (*Acinetobacter* spp.)	35.7 (3.3–75.5)	55.8 (4.2–167.1)
AUC_∞/MIC (h) (*Pseudomonas* spp.)	8.2 (5.9–13.9)	17.8 (12.1–22.2)
Mean residence time (h)	3.0 (1.7–6.7)	4.0 (2.1–7.7)
$C_{min,ss}$	NA	0.5 (0.1–2.0)
$C_{av,ss}$	NA	2.0 (0.6–3.3)
Accumulation index	NA	1.2 (1.0–1.6)

PK, Pharmacokinetic; C_{max}, maximum concentration; AUC_8, area under concentration-time curve from zero to 8 h; AUC_∞, area under concentration-time curve from zero to infinity; $t_{1/2}$, elimination half life; V_d, volume of distribution; CL, clearance; MIC, minimum inhibitory concentration; $C_{min,ss}$, trough concentration at steady-state; NA, not applicable; $C_{av,ss}$, average concentration at steady-state; NA, not available

[a] Data are reported as the median value, with the range given in parenthesis

The single-dose and steady-state C_{max} [median (range): 4.6 (2.5–23.1) vs. 5.4 (1.8–21.8) μg/ml, respectively] in our study were lower than those reported in patients with cystic fibrosis [21.4 (5) vs. 23 (8) mg/l, respectively) [21]. One possible explanation is the higher volume of distribution seen in critically ill patients [27]. The volume of distribution in the patients included in our study [median (range)] was 0.3 (0.2–0.5) after both the single dose and at steady-state as compared to cystic fibrosis patients [0.09 (0.02) vs. 0.09 (0.03) l/kg, respectively) [21].

Colistin exhibits concentration-dependant bactericidal activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [11, 28]. However, there is no consensus on the optimal C_{max}/MIC ratio for colistin [18], whereas for the other concentration-dependent bactericidal antibiotics, an optimal C_{max}/MIC ratio of 8–10 is recommended [29, 30]. The median (range) C_{max}/MIC value in our study following the single dose and at steady-state was 13.4 (1.3–40.3) and 26.3 (0.9–64.9), respectively, for *Acinetobacter* spp. and 3.2 (1.6–23.1) and 3.8 (2.3–10.9), respectively, for *Pseudomonas* spp.. Among those patients whose cultures grew *Acinetobacter* spp., MIC and C_{max} values were available for nine patients following the single dose and for eight patients at steady-state. Of these, seven each had a C_{max}/MIC ratio of >8. Of the four patients whose cultures grew *Pseudomonas* spp., one each had a C_{max}/MIC ratio of >8 after the single dose and at steady-state, indicating that higher dosing may be required for patients with *Pseudomonas* spp. infection.

The dose and dosing frequency of colistimethate sodium was determined in this study taking into consideration body weight and CL_{CR} (as per the product insert). None of our patients had a CL_{CR} of <20 ml/min, and therefore the dosing was primarily based on weight. The four patients who weighed≤60 kg received a considerably smaller dose of colistimethate sodium (2.5 M IU/day and 2.75 M IU/day in two patients each) and three of the four succumbed. In contrast, nine of the 11who weighed>60 kg and received 6 MIU/day survived, indicating that adequate dosing is necessary for best results. It is important to note that among the many factors that were tested for their association with survival in our study, only the dose of the drug was found to be significantly associated. The C_{max}/MIC ratios obtained in our study for both the organisms reiterate this observation. One of the major reasons for colistin going into disrepute was safety concerns. Our study indicates that the use of doses up to 6 MIU/day is safe even in critically ill patients, thereby corroborating the findings from recent reviews by Florescu et al. [26] and Couet et al [31]. Other authors have reported the safe use of colistimethate sodium even at doses of 9 MIU per day [32] and with a loading dose of 6 MIU

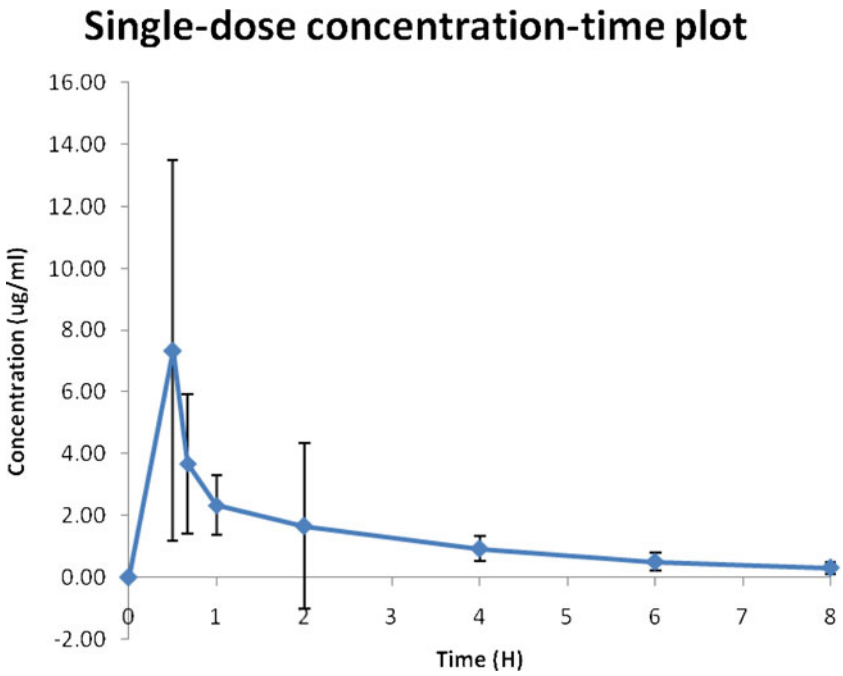

Fig. 1 Single-dose time-concentration plot of colistin (n=13). Data are presented as the mean and standard deviation (SD; *whiskers*)

[33]. It would appear relevant to suggest changes to the label so that dosing is based on CL_{CR} only and not also on body weight.

The main limitations of our study are that (1) we did not measure urinary concentrations of colistin and therefore could not determine renal clearance, (2) the multivariate analysis is limited by the fact that the baseline diagnosis which itself influences prognosis is not taken for consideration due to small sample size and (3) the survival analysis was carried out following completion of the study.

Conclusion

Among the patients enrolled in our study, colistin was well tolerated, and no events of either renal toxicity or neurotoxicity were noted at the dose administered. C_{max} was found to be comparable to that of previous studies but appears to be inadequate to maintain the C_{max}/MIC ratio to an optimal level—at least for *Pseudomonas* spp. Dose revision may need to be considered for patients weighing≤60 kg. Overall, the pharmacokinetic–pharmacodynamic information obtained

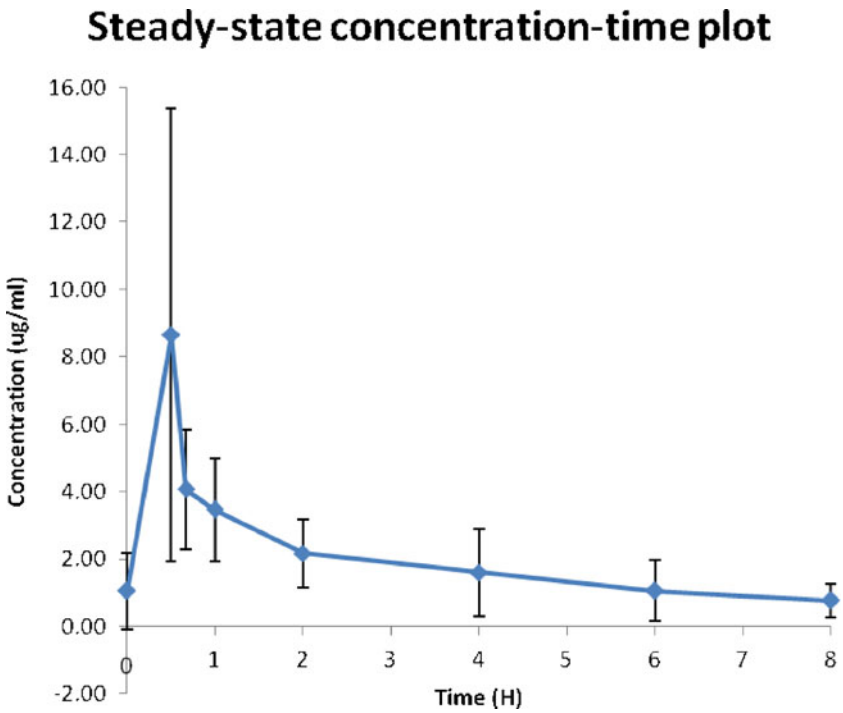

Fig. 2 Steady-state time-concentration plot of colistin (n=11). Data are presented as the mean and SD (*whiskers*)

from this study may be a useful tool in antibiotic selection and implies therapeutic benefits of colistin in hospital-acquired MDR Gram-negative bacilli infections.

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Conflict of interest SPJ, RDN and JAG are employees of Cipla pharmaceuticals Ltd. RKN is an employee of Sitec Labs (Pvt.) Ltd.

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