High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

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Background. Gram-negative bacteria susceptible only to colistin (COS) are emerging causes of severe nosocomial infections, reviving interest in the use of colistin. However, consensus on the most effective way to administer colistin has not yet been reached.

Methods. All patients who had sepsis due to COS gram-negative bacteria or minimally susceptible gram-negative bacteria and received intravenous colistimethate sodium (CMS) were prospectively enrolled. The CMS dosing schedule was based on a loading dose of 9 MU and a 9-MU twice-daily fractioned maintenance dose, titrated on renal function. For each CMS course, clinical cure, bacteriological clearance, daily serum creatinine clearance, and estimated creatinine clearance were recorded.

Results. Twenty-eight infectious episodes due to *Acinetobacter baumannii* (46.4%), *Klebsiella pneumoniae* (46.4%), and *Pseudomonas aeruginosa* (7.2%) were analyzed. The main types of infection were bloodstream infection (64.3%) and ventilator-associated pneumonia (35.7%). Clinical cure was observed in 23 cases (82.1%). Acute kidney injury developed during 5 treatment courses (17.8%), did not require renal replacement therapy, and subsided within 10 days from CMS discontinuation. No correlation was found between variation in serum creatinine level (from baseline to peak) and daily and cumulative doses of CMS, and between variation in serum creatinine level (from baseline to peak) and duration of CMS treatment.

Conclusions. Our study shows that in severe infections due to COS gram-negative bacteria, the high-dose, extended-interval CMS regimen has a high efficacy, without significant renal toxicity.

Severe nosocomial infections due to multidrug-resistant (MDR) gram-negative bacteria account for high morbidity and mortality [1]. The increasing incidence of

infections due to these strains and the lack of effective antimicrobials in the drug-development pipeline [2] has rekindled interest in the use of colistin as "last-line" therapy [3]. However, in vitro efficacy of colistin against MDR *Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Klebsiella pneumoniae* (97%, 96%, and 88%, respectively) [4] does not entail clinical cure, which, in severe infections due to strains susceptible to colistin only (COS), ranges from 15% to 75% [5–14]. Although this wide range of in vivo efficacy mainly depends on substantial heterogeneity of illness severity, the role of dosing regimen must be taken into account. The benefit of administering the right drug is often nullified by suboptimal drug exposure at the infection site due to inadequate dosage. Despite >50 years of clinical use,

consensus on the most effective colistin dosage has not yet been reached [3]. Colistin exhibits a concentration-dependent bactericidal activity, and its therapeutic efficacy strictly depends on the ratio of peak level to minimum inhibitory concentration (MIC) or the ratio of area under the curve to MIC [15, 16]. In critically ill patients, current colistin dosing regimens result both in subtherapeutic peak concentration with respect to MDR gram-negative bacteria MIC break points [17–20] and in prolonged time to steady state [19, 20], leading to suboptimal and delayed effective treatment. Therefore, strategies involving higher doses and longer dosing-intervals, along with loading doses, have been proposed to obtain a more effective killing [17–21]. However, clinical efficacy and renal toxicity of such regimens remain to be tested.

The purpose of this study was to test the renal toxicity along with efficacy of a salvage therapy with a high-dose and extended-interval dosing regimen of colistin in a cohort of critically ill patients with nosocomial infections due to COS gram-negative bacteria.

METHODS

Study Population and Data Collection

A prospective, observational, cohort study was performed from August 2010 to June 2011 in a 16-bed general intensive care unit (ICU) at a teaching hospital. All critically ill patients who had sepsis due to COS or minimally susceptible gram-negative bacteria and were administered intravenous colistimethate sodium (CMS) as a rescue therapy were enrolled. Patients were excluded if they were <18 years old, pregnant, or breastfeeding, or if they received colistin treatment for <72 hours. Patients who, after a cured infectious episode, received a second colistin course due to infection with another COS gram-negative bacteria were considered as 2 different cases. Patients were followed up until ICU discharge or death. Primary outcomes were colistin nephrotoxicity and efficacy.

A standardized case form was used to record patient characteristics, including age, sex, weight, underlying comorbidities (evaluated by Charlson comorbidity index), Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, Sequential Organ Failure Assessment (SOFA) score on enrollment, type of infection, causative organism and in vitro susceptibility, daily doses and duration of colistin therapy, cumulative dose of colistin, coadministered antibiotics, nephrotoxic agents (aminoglycosides, vancomycin, nonsteroidal anti-inflammatory drugs, intravenous radiocontrast agent, diuretics, mannitol), and clinical and microbiological responses to therapy.

Definitions and Microbiological Testing

Infections were defined according to the Centers for Disease Control and Prevention (CDC) [22]. Ventilator-associated pneumonia (VAP) was defined according to American Thoracic Society/Infectious Diseases Society of America guidelines [23], and its bacteriological diagnosis required at least 10^6 colony-forming units per milliliter in a quantitative tracheal aspirate culture. Sepsis, severe sepsis, and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria [24].

Follow-up specimens from tracheal aspirates, urine, blood, and other suspected sites of infection were obtained twice weekly and, when clinically indicated, from the start of CMS therapy until discharge or death. Identification of all causative microorganisms was based on routine microbiological methods. Antimicrobial susceptibility testing was performed by MicroScan Walkaway System, using 42 GNC panels (Siemens, New York, NY) and break points were those defined by the Clinical and Laboratory Standards Institute [25]. Susceptibility to colistin was determined by the Etest (BioMerieux, Marcy l'Etoile, France), using cation-adjusted Mueller-Hinton agar, and the isolates were considered susceptible if the MIC was ≤2 mg/L [25].

An isolate was defined as COS if it was fully susceptible to colistin but resistant to antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, and aminoglycosides. MDR isolates fully susceptible to colistin and with full or intermediate susceptibility to aminoglycosides were considered minimally susceptible to antibiotics [11].

Colistin Administration

Colistin was administered as CMS (Colomycin; Forest Laboratories, Bextley, United Kingdom) dissolved in 100-mL sterile saline and was given over 30 minutes.

According to recent data [8, 15, 17–21], patients received a loading CMS dose of 9 MU, followed by a maintenance dose of 4.5 MU every 12 hours. In patients with moderate-to-severe renal impairment (creatinine clearance rate, <50 mL/min), dose and dosing intervals adjustments were made according to Cockcroft and Gault creatinine clearance estimates: after a loading dose of 9 MU, maintenance doses of 4.5 MU/24 hours (for creatinine clearance rate in the 20–50 mL/min range) or 4.5 MU/48 hours (for creatinine clearance rate of <20 mL/min) were administered.

Efficacy and Nephrotoxicity Assessment

Efficacy was evaluated by both clinical and bacteriological responses to therapy. Clinical cure and failure were defined as resolution and persistence/worsening, respectively, of symptoms and signs of infection. Bacteriological clearance and failure were defined as eradication or persistence, respectively, of COS gram-negative bacterial isolates on follow-up cultures,

regardless of the clinical outcome of infection. Two independent investigators evaluated type of infection and outcome.

Daily serum creatinine level and estimated creatinine clearance rate were recorded from the first day of CMS therapy until discharge or death. Baseline glomerular filtration rate (GFR) was calculated by the abbreviated Modification of Diet in the Renal Disease equation [26]. In patients with normal renal function (baseline serum creatinine level <1.2 mg/dL or GFR ≥50 mL/min/1.73 m^2), nephrotoxicity was defined as doubling of baseline serum creatinine level or drop in baseline creatinine clearance rate by ≥50%, while in patients with baseline renal dysfunction (serum creatinine level ≥1.2 mg/dL or GFR <50 mL/min/1.73 m^2), nephrotoxicity was defined as an increase by >50% of the baseline S_{CR} level, a decrease by ≥20% from the serum creatinine clearance rate calculated at baseline, or need of renal replacement therapy [7, 9]. Criteria need to be fulfilled for at least 2 consecutive determinations 24 hours apart, after ≥2 days of CMS therapy. The Acute Kidney Injury Network criteria [27] were used to evaluate the severity of acute kidney injury (AKI).

Statistical Analysis

Serum creatinine level and creatinine clearance rate at baseline (ie, start of CMS therapy), peak (ie, worst level reached during treatment), the end of CMS therapy, and the end of follow-up were considered for statistical analysis. Continuous normally distributed data are expressed as mean (± SD) and compared using the unpaired Student t test. Nonnormally distributed data are expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical data are expressed as number and percentage of events and compared using the Fisher exact test. A Pearson regression analysis was performed to clarify the association between variables. In all comparisons, a P value <.05 was considered statistically significant. Data were analyzed using SPSS, release 5.0.1 for Windows (Chicago, IL).

RESULTS

Characteristics of the Whole Sample

Out of 28 critically ill patients who were prescribed colistin for COS gram-negative bacterial infections, 3 were excluded because CMS treatment duration was <72 hours (because of discharge, for 2 patients, and death, for 1). Three patients developed 2 infectious episodes due to different species of COS pathogens, and each infection was included as a separate case. Therefore, a total of 28 CMS treatments in 25 patients were analyzed.

Patients were predominantly males (75%), with a mean age of 65 ± 18 years. Main comorbid conditions were hypertension (54.2%), ischemic heart disease (45.8%), diabetes mellitus (25%), chronic obstructive pulmonary disease (12.5%), and chronic

kidney disease (8.3%). Mean Charlson comorbidity index was 2.7 ± 1.8. Mean APACHE II score was 18 ± 6. Mean SOFA score on day 1 of CMS therapy was 8 ± 2. All patients underwent mechanical ventilation. Median onset time of first infectious episode was 26 days (IQR, 18–48 days) from ICU admission.

In 16 of 28 infectious episodes (57.1%) clinical presentation was severe sepsis, while in the other 12 (42.9%) it was septic shock. Bloodstream infections (BSIs) occurred in 18 (64.3%) cases, and VAP occurred in the remaining 10 (35.7%) cases. Pathogens were *A. baumannii* in 13 (46.4%), *K. pneumoniae* in 13 (46.4%), and *P. aeruginosa* in 2 (7.2%) episodes. All strains were fully susceptible to colistin, with MICs of 0.19–1.5 mg/L, while 8 isolates of *K. pneumoniae* were susceptible also to gentamicin. Thus, 20 of the gram-negative bacterial isolates were COS, while the remaining 8 were considered minimally susceptible strains.

In 14 episodes (50%) CMS was administered as monotherapy, and in 14 (50%) it was employed as combination therapy with aminoglycosides (69.2%) or carbapenems (30.8%).

In 22 episodes, patients with normal baseline renal function (serum creatinine level, 0.7 ± 0.2 mg/dL) received CMS at daily and cumulative doses of 8.5 MU/day (IQR, 7.6–9 MU/day) and 99 MU/course (IQR, 69–126 MU/course), respectively. Median duration of treatment was 12 days (IQR, 10–17 days). In 6 episodes, patients with abnormal baseline renal function (serum creatinine level, 3.2 ± 1.3 mg/dL) received a daily dose of medication of 6.7 MU/day (IQR, 3.5–8 MU/day) and a cumulative dose of 61 MU/course (IQR, 28–89 MU/course). In this subset, the median duration of CMS administration was 10.5 days (IQR, 8–18 days).

CMS Efficacy

Clinical cure was obtained in 23 infectious episodes (82.1%). Patients characteristics and clinical features of infectious episodes with favorable and unfavorable therapeutic response are summarized in Table 1. Bacteriological clearance was achieved in 73.9% (17) of the cured infectious episodes, by the third day (IQR, days 1–5) of CMS therapy in all BSIs, and by the eighth day (IQR, days 3–10) in 4 (40%) VAP episodes. No recurrent infection by the same multiresistant pathogen was observed. Colistin resistance was never observed during the follow-up period. Breakthrough superinfections by intrinsically colistin-resistant organisms (*Serratia marcescens* and *Proteus mirabilis*) were observed in 2 patients on days 12 and 14 of CMS treatment.

CMS Nephrotoxicity

No deterioration of renal function was observed during 23 CMS treatment courses (82.1%). In this subset, the nonsignificant increase of serum creatinine levels observed during treatment (0.3 mg/dL [IQR, 0.12–0.57 mg/dL]) returned at baseline at the end of the follow-up period (0.7 vs 0.7 mg/dL).

Table 1. Patients' Characteristics and Clinical Features of Infectious Episodes Among 23 Infectious Episodes With and 5 Without a Favorable Response to Colistimethate Sodium Therapy

Variable	CMS Response[a]	No CMS Response
Age (years), mean ± SD	62 ± 18	76 ± 3
Charlson comorbidity index, mean ± SD	2 (1.5)	3.2 (2.2)[b]
Surgical admission, No. (%) of patients	8/20 (40)	4/5 (80)
APACHE II score, mean ± SD	18 ± 6	25 ± 7[b]
SOFA score, mean ± SD	7.6 ± 2	9.1 ± 2
ICU LOS (days)	56 (30–85)	75 (52–86)
ICU mortality, No. (%) of patients	5/20 (25)	5/5 (100)[b]
Infectious episodes, No. (%) of cases	23/28 (82.1)	5/28 (17.9)
Onset time of infection (days)	22 (12–47)	42 (23–54)
BSI, No. (%) of cases	13/23 (56.5)	5/5 (100)
BSI-associated pathogens, No. of isolates		
Acinetobacter baumannii	6	2
Klebsiella pneumoniae	6	3
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	13/13 (100)	0/5[b]
VAP, No. (%) of cases	10/23 (43.5)	0/5
VAP-associated pathogens, No. of isolates		
Acinetobacter baumannii	5	0
Klebsiella pneumoniae	4	0
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	4/10 (40)	0/5 (0)
Clinical presentation, No. (%) of cases		
Severe sepsis	16/23 (69.5)	0/5 (0)[b]
Septic shock	7/23 (30.5)	5/5 (100)[b]
Daily CMS dose (MU/d)	8.5 (7.3–9)	7.7 (5–8.5)
Cumulative CMS dose (MU/course)	91 (61–122)	105 (17–142)
CMS monotherapy, No. (%) of courses	12/23 (52.2)	2/5 (40)
CMS treatment duration (days)	11 (10–14.5)	15.5 (7–21)

Data are median value (interquartile range), unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CMS, colistimethate sodium; ICU, intensive care unit; LOS, length of stay; MU, million units; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

[a] Three patients developed 2 infectious episodes due to different species of pathogens susceptible only to colistin. Each infection was considered to be a second case and was treated with CMS separately.

[b] $P < .05$ versus patients with response.

Figure 1. Estimated median creatinine clearance values on the first day of colistin treatment (baseline), at the lowest value reached (worst), on discontinuation of colistimethate sodium (CMS) treatment (stop CMS), and at the end of follow-up (final), in patients without (white box plots) and those with (gray box plots) acute kidney injury (AKI). *$P < .05$ versus baseline. Abbreviations: AKI, acute kidney ijury; CMS, colistimethate sodium.

AKI developed during 5 CMS treatment courses (17.8%) in 5 different patients (one with preexisting renal dysfunction), with an onset time of 7 days (IQR, 5.5–8.5 days). In these patients, the serum creatinine level at the beginning of therapy was 0.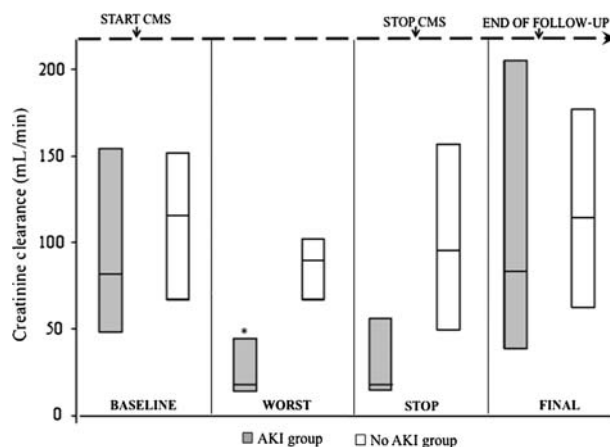95 mg/dL (IQR, 0.59–1.37 mg/dL) and peaked at 4.1 mg/dL (IQR, 2.09–5.85 mg/dL; $P = .036$ vs. baseline) within a median of 4 days (IQR, 2.5–5 days). At the end of CMS therapy the serum creatinine level was 3.73 mg/dL (IQR, 0.64–5 mg/dL), and during follow-up it dropped to 1.16 mg/dL (IQR, 0.55–3.68 mg/dL; $P = .53$ vs baseline) within a median of 9.5 days (IQR, 7–13 days) from CMS discontinuation. Temporal trends of estimated creatinine clearance rates in patients with and those without AKI are reported in Figure 1. All cases involved nonoliguric episodes, and in no patients was renal replacement therapy deemed necessary. One, two, and two patients met the criteria for AKI stages I, II, and III, respectively. All patients completed CMS therapy by dose reduction.

Mean age (63.7 ± 18 vs 72 ± 8 years), mean Charlson comorbidity index (2.2 ± 1.6 vs 2.7 ± 1.8), and chronic kidney disease (22% vs 20%) did not differ between patients with and patients without AKI. Apart from AKI associated with use of radiocontrast agents, no significant predictor of renal impairment was found in univariate analysis (Table 2).

Overall, no correlation was found between variation in serum creatinine levels (percentage change from baseline to peak) and daily ($y = 1 \times 10^{-6}x + 90.064$; $r = 0.004$; $P = .98$) (Figure 2) and cumulative ($y = 0.0003x + 60.123$; $r = 0.06$; $P = .759$) doses of CMS, as well as between variation in serum creatinine levels (percentage change from baseline to peak) and duration of CMS treatment ($y = -1.247x + 107.9$; $r = -0.058$; $P = .77$) (Figure 2).

DISCUSSION

The main finding of the present study is that, in critically ill patients with life-threatening nosocomial infections due to

Table 2. Potential Risk Factors for Acute Kidney Injury Associated With Colistimethate Sodium Therapy

Factor	No AKI (n = 23)	AKI (n = 5)
Septic shock	10 (43.5)	2 (40)
Concomitant nephrotoxic agents	20 (86.9)	4 (80)
Antibiotics	7 (30.4)	3 (60)
Diuretics	15 (65.2)	3 (60)
Radiocontrast agents	1 (4.3)	4 (80)[a]
Mannitol	4 (17.4)	1 (20)
Daily CMS dose (MU/day)	8.3 (6.5–9)	7.1 (6–8.5)
CMS treatment duration (days)	11 (9.5–17.5)	12 (10–15)
Cumulative CMS dose	92 (56–126)	81 (64–92)

Data are No. (%) of infectious episodes or median (interquartile range).

Abbreviations: CMS, colistimethate sodium; MU, million units.

[a] $P < .05$ between groups.

COS gram-negative bacteria, rescue therapy with a high-dose, extended-interval dosing regimen of colistin provides a high degree of clinical cure, with no significant renal toxicity.

Currently, COS *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* are emerging causes of severe nosocomial infections in the ICU [28], and the daily total CMS dose is directly related to clinical cure. Increasing the daily dose from 2 MU [7] to 9 MU [5] improves clinical cure rates from 51% [7] to 70% [5], respectively. However, not only daily dose, but also fractioning may affect efficacy. A fractioned CMS regimen of 9 MU 3 times daily, currently prescribed in ICU practice, has been associated with suboptimal and delayed steady-state concentrations [20, 21]. Therefore, a loading dose to rapidly achieve target drug concentration and a dosing schedule that uses high single doses at longer intervals has been proposed [17, 18, 20, 21]. On the basis of this pharmacokinetic/pharmacodynamic background and severity of infection, we adopted a CMS dosing schedule that involved a loading dose of 9 MU and a maintenance dose of 4.5 MU every 12 hours [21]. This regimen is consistent with data by Garonzik et al. [20], who, on the basis of pharmacokinetic analysis of CMS and colistin in critically ill patients, suggest that to obtain a colistin steady-state plasma concentration of 2.5 mg/L, a 70-kg patient with a creatinine clearance rate of 80 mL/minutes needs to receive a CMS loading dose of 10 MU, followed by a maintenance CMS daily dose of 10 MU.

Our dosing regimen resulted in a clinical cure rate of 82%, which is above the best favorable response rates reported in similar ICU settings with lower single doses and/or more fractioned regimens [4–14]. Although the effectiveness of colistin in pneumonia has been questioned because of its inadequate lung diffusibility [9, 14], in our cohort clinical cure was attained in 100% of VAP cases. The high single-dose CMS dosing strategy may have contributed to this high response rate, by increasing the colistin concentration in the infected lung tissue. This hypothesis well fits with results of previous studies that reported a cure rate of only 57% in COS *P. aeruginosa* VAP treated with a 2.2–4.3-MU daily CMS regimen [9] and a cure rate of 75% in COS *A. baumannii* VAP episodes treated with a 6-MU daily CMS regimen [14]. Of note, however, bacteriological clearance in VAP patients was only 40%. This low rate may reflect the well-known persistent artificial and native airway colonization with Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa*, despite therapeutic success, and may explain why clinical features and quantitative cultures of bronchial aspirate are the most relevant parameters in evaluating therapeutic response in patients with VAP [29].

Since current reported rates of renal failure may reach 50% [30, 31], colistin-related nephrotoxicity still remains a major concern. Colistin induces tubular damage by increasing the membrane permeability of epithelial cells, leading to leakage of contents and cell death [32]. This effect has been related to drug concentration and treatment duration [33, 34], with a significant relationship between creatinine increase and cumulative dose of CMS [35]. In our study, de novo AKI was observed only in 18% of CMS courses, a percentage similar to those reported for lower single doses and more fractioned regimens of CMS [7, 13, 35]. Consistent with previous reports adopting the same AKI definition [7, 10, 22], in our sample AKI occurred early, was not severe, did not cause discontinuation of CMS, and subsided rapidly. In contrast to other reports [34–36], in our study renal damage did not depend on daily CMS doses, duration of treatment, or cumulative CMS doses. Titration of dose on the basis of renal function by prolonging dosing interval, instead of by reducing the single dose (according to colistin's concentration-dependent pharmacodynamic behavior), may have contributed to the low rate and moderate severity of AKI [20]. This fits well with a recent hypothesis [37] that attributes CMS nephrotoxicity to the minimum plasma concentration of colistin, as already demonstrated for aminoglycosides [38]. However, because of the relatively small number of patients, the study cannot provide an accurate estimate of the relative contribution of colistin to renal dysfunction. Other factors with a potentially crucial role in affecting kidney function include age, race, comorbidities, severity of critical illness, hemodynamic status, and possible receipt of other coadministered nephrotoxic agents, such as radiocontrast medium. Nevertheless, even in presence of these favoring factors, the absolute rate of AKI was low.

Some points of the study need to be underlined. Although colistin monotherapy and extended-dose-interval regimens may promote colistin resistance in presence of colistin-
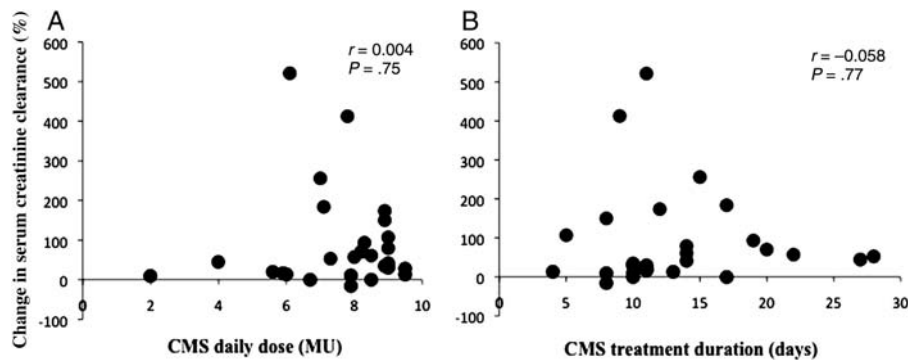
Figure 2. Correlation between serum creatinine variation (from baseline to peak values) and daily colistimethate sodium doses (*A*) and between serum creatinine variation (from baseline to peak values) and treatment duration (*B*). Abbreviation: CMS, colistimethate sodium.

heteroresistant gram-negative bacteria [15], in our study colistin monotherapy was used in 50% of cases with no evidence of resistance emergence during and after CMS therapy discontinuation, as evaluated by surveillance cultures. Moreover, it is difficult to say whether combination treatment with carbapenems or other active drugs played a more important role than giving a high dose of colistin. However, no differences were found in clinical cure for combination therapy regimens as compared to monotherapy, according to a recent comprehensive review [39].

Our study has some limitations. Despite the prospective design, the relatively small number of studied patients and the absence of a control group represent major limitations. Data on possible side effects of CMS apart from nephrotoxicity were not evaluated actively. Finally, serum concentrations of colistin were not measured, and therefore we cannot draw any conclusion regarding peak levels reached with our dosing regimen.

In conclusion, this study clearly shows that a 9-MU twice-daily fractioned dosing regimen of colistin, along with a 9-MU loading dose, can be used with satisfactory efficacy and relatively low nephrotoxicity in life-threatening infections caused by COS gram-negative bacteria, provided that an ongoing adaption of dosing regimen to renal function is ensured. A multi-center study, with proper study design and a relevant control group, is needed to confirm these preliminary data and to better define the relationships between colistin blood levels obtained by the high-dose, extended-interval dosing strategy and renal toxicity.

Note

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