MAJOR ARTICLE

Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study

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Background. Critically ill patients with severe sepsis or septic shock may need relatively high colistin daily doses for efficacy against multidrug-resistant and extensively drug-resistant gram-negative rods. However, acute kidney injury (AKI) may represent a major dose-limiting adverse effect of colistin. We sought to determine AKI occurrence and to identify factors influencing AKI risk in severely ill patients receiving colistin according to a recently proposed dosing strategy.

Methods. A prospective, observational, cohort study involving patients with severe sepsis or septic shock who received colistin was performed. AKI was defined according to Acute Kidney Injury Network criteria. Colistin administration was driven by a modified pharmacokinetics-pharmacodynamics (PK/PD)–based dosing approach.

Results. Of 70 patients who received colistin at a median daily dose of 9 million IU (MIU; interquartile range, 5.87–11.1 MIU), 31 (44%) developed AKI. In univariate analysis, age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA), score and baseline renal impairment were significantly associated with AKI. Moreover, patients with AKI were less frequently treated with adjuvant ascorbic acid ($P = .003$). In multivariate analysis, independent predictors of AKI were baseline renal impairment (adjusted hazard ratio, 4.15; 95% confidence interval, 1.9–9.2; $P < .001$) and age (1.03; 1.0–1.05; $P = .028$), whereas a strong independent renal-protective role emerged for ascorbic acid (0.27; .12–.57; $P < .001$).

Conclusions. In severely ill patients receiving colistin according to a PK/PD-driven dosing approach, baseline renal impairment and older age strongly predict AKI occurrence, but concomitant administration of ascorbic acid markedly reduces AKI risk, allowing safer use of colistin.

Keywords. colistin; colistimethate sodium; acute kidney injury; ascorbic acid; critically ill.

Colistin is one of the few options for treating severe infections by multidrug-resistant and extensively drug-resistant (XDR) gram-negative bacteria. Owing to its bactericidal effect, which is both concentration and time dependent [1], colistin efficacy also depends on appropriate exposure, which may require relatively high daily doses in critically ill patients [2]. However, acute kidney injury (AKI) is a major dose-limiting adverse effect of colistin [2, 3], particularly in patients who are per se at high risk for AKI because of the interplay between predisposing conditions (eg, advanced age, volume depletion, chronic kidney disease, diabetes mellitus, cancer, and anemia) and exposure to multiple harmful events to the kidneys (eg, critical illness, sepsis, shock, burn, trauma, major surgery, and nephrotoxin exposure) [4]. In this setting, attempts to risk stratification by identifying relevant modifiers of renal toxicity may help physicians cautiously balance each patient's need for optimal dosing of nephrotoxic drugs and risk of AKI [4].

Although risk factors for colistin-induced AKI have been identified [5–10] and models to predict nephrotoxicity

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have been proposed [11], few studies have specifically focused on severely ill patients receiving colistin at higher daily doses than those usually employed in Europe [3, 12, 13]. The aim of the current study was to assess the incidence of colistin-related AKI and identify factors influencing its occurrence in critically ill patients with severe sepsis and/or septic shock receiving colistin according to a modified pharmacokinetics-pharmacodynamics (PK/PD)–driven dosing approach [2].

METHODS

Study Design, Setting, and Patient Population

A prospective, observational, cohort study was performed in critically ill adult patients (≥18 years old) who received intravenous colistin because of severe sepsis and/or septic shock [14] and were consecutively admitted to a 16-bed mixed intensive care unit at a teaching hospital between November 2012 and October 2014. Patients were excluded if they received colistin for <72 hours, developed AKI within 48 hours after starting colistin, or were receiving renal replacement therapy (RRT) at the beginning of colistin therapy. For patients receiving multiple colistin courses, only the first treatment was considered.

Colistin was administered as intravenous colistimethate sodium (CMS) (Colomycin; Forest Laboratories) dissolved in 100-mL sterile saline solution for 30 minutes. Throughout this article, the term *colistin* refers to CMS, and dosing is expressed in international units of the prodrug (1 million IU [MIU] of CMS equals 30 mg of colistin base activity [CBA]). Colistin dosing was driven by an institutional protocol, based on a dosing algorithm developed for critically ill patients [2]. Colistin loading dose by ideal body weight (IBW) or actual body weight (ABW), whichever was lower, was targeted to a steady-state concentration of 2.5 mg/L, using the following equation: Loading Dose (IU) = (2.5 × 2 × Body Weight) × 30 000 (maximum dose, 9 MIU).

The maintenance dose was titrated to creatinine clearance (CrCl) and to a target steady-state concentration of 2.5 mg/L, according to the following equation: Daily Maintenance Dose (IU) = 2.5 × [(1.5 × CrCl) + 30] × 30 000 [2]. For CrCl of 60–130 mL/min/1.73 m^2, a fixed daily dose of 9 MIU was administered [2]. For CrCl >130 mL/min/1.73 m^2, a daily dose of 10–12 MIU was allowed, by balancing risk of colistin underexposure (eg, high-inoculum or deep-seated infections, high colistin minimum inhibitory concentration [MIC] values of isolates, or very high CrCl) and coexistence of known risk factors for AKI (eg, advanced age, comorbid conditions, or coadministration of nephrotoxic drugs). The maintenance dose was administered twice a day, starting 12 hours after the loading dose, and was daily titrated according to renal function. Inhaled colistin (2 MIU thrice daily) was allowed for patients with pneumonia.

All patients were treated according to grade 1 recommendations of the Surviving Sepsis Campaign [15] and received vitamin D supplementation per protocol; grade 2 recommendations (eg, low dose hydrocortisone for refractory septic shock and prone positioning for severe acute respiratory distress syndrome) [15] and use of intravenous ascorbic acid as adjuvant therapy for sepsis were at the discretion of the attending physician. Antimicrobial susceptibility was tested using the Vitek 2 system (bioMerieux). Susceptibility to colistin was determined by means of Etest (bioMerieux), using cation-adjusted Mueller–Hinton agar. Breakpoints were those defined by the European Committee on Antimicrobial Susceptibility Testing [16].

Study Variables and Definitions

Recorded parameters included the following: age, sex, body weight (ABW and IBW), Charlson Comorbidity Index, type of admission (surgical or medical), Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission, Sequential Organ Failure Assessment (SOFA) score at the beginning of the colistin course, type and cause of infection, colistin MIC for the isolates, daily serum creatinine (SCr) level, CrCl and diuresis, baseline renal impairment, daily dose (total and by IBW and ABW), and duration of colistin therapy, cumulative colistin dose, coadministered antibiotics and nephrotoxic agents (aminoglycosides, vancomycin, nonsteroidal anti-inflammatory drugs, intravenous dye, loop diuretics, amphotericin B, and acyclovir), low-dose hydrocortisone, adjuvant therapy with ascorbic acid, infection outcome (clinical resolution or failure), and renal recovery.

Severe sepsis, septic shock, and type of infection were defined according to standardized criteria [14, 17, 18]. Clinical resolution and failure were defined as resolution and persistence/worsening, respectively, of symptoms and signs of infection [14, 17, 18].

Baseline renal impairment was defined as a glomerular filtration rate <50/mL/min/1.73 m^2 before starting colistin therapy. This rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [19]. CrCl was estimated using the method described by Jelliffe [20]. AKI was defined as an increase in SCr level to ≥1.5 times baseline or by ≥0.3 mg/dL within a 48-hour period, according to Acute Kidney Injury Network (AKIN) criteria [4], after ≥2 days of colistin therapy. Before applying the criteria, hypovolemia and urinary tract obstruction, if present, were treated. AKI was staged for severity according to the greatest change in SCr level observed during the whole colistin course, as follows: stage 1, increase in SCr level to 1.5–1.9 times baseline or by ≥0.3 mg/dL; stage 2, increase to 2.0–2.9 times baseline; stage 3, increase to 3.0 times baseline or by ≥4 mg/dL or need for RRT [4]. AKI was assessed daily until the end of colistin therapy or death, whichever came first. Renal recovery was defined as the return to baseline Scr levels (±50%) and was assessed up to 2 weeks after the end of therapy.

The median daily dose that the patient had received before meeting AKIN criteria was used to assess the relationship

Table 1. Univariate Analysis of Risk Factors for Colistin-Induced AKI

Variable	AKI Group (n = 31)	No-AKI Group (n = 39)
Age, median (IQR), y	70 (59–78)	58 (37–72)[a]
Male sex, No. (%)	22 (71)	22 (56.4)
IBW, median (IQR), kg	66 (57–60.5)	65 (60–70.5)
ABW, median (IQR), kg	75 (70–85)	71 (64–80)
Charlson Comorbidity Index, median (IQR)	2 (1–4)	1 (0–4)
Surgical admission, No. (%)	17 (54.8)	25 (64)
APACHE II score at ICU admission, median (IQR)	23 (17–27)	19 (13–24)[a]
SOFA score on day 1 of colistin treatment, median (IQR)	9 (7–10)	7 (5–9)[a]
Type of infection, No. (%)		
Ventilator-associated pneumonia	16 (51.6)	21 (53.8)
Bloodstream infection	13 (41.9)	16 (41)
Urinary tract infection	2 (6.4)	2 (5.1)
Septic shock, No. (%)	18 (58)	20 (51.3)
Administered CMS total daily dose, median (IQR), MIU		
During whole CMS course	6.5 (4.75–9)	9 (8–12)[a,b]
Before AKI onset	8 (6–9)	. . .
After AKI onset	5.5 (4–6.5)	. . .
Administered CMS daily dose by IBW, median (IQR), IU/kg		
During whole CMS course	100 130 (75 800–127 700)	156 500 (127 400–168 200)[a,b]
Before AKI onset	124 770 (93 600–136 500)	. . .
After AKI onset	83 600 (60 000–100 130)	. . .
Administered CMS daily dose by ABW, median (IQR), IU/kg		
During whole CMS course	78 570 (66 700–112 000)	135 740 (110 000–158 250)[a,b]
Before AKI onset	105 000 (80 000–126 000)	. . .
After AKI onset	66 700 (53 600–87 500)	. . .
Colistin treatment duration, median (IQR), d	14 (10–16)	14 (11–20)
Administered CMS cumulative dose, median (IQR), MIU		
During whole CMS course	84 (50–115)	144 (104–180)[a]
Before AKI onset	44 (30–96)	. . .
After AKI onset	32 (24–48)	. . .
Clinical resolution, No. (%)	23 (74.2)	31 (79.5)
Baseline renal impairment, No. (%)	13 (41.9)	5 (12.8)[a]
Baseline CrCl, median (IQR), mL/min/1.73 m^2	67 (36–78)	133 (82–182)[a]
Baseline SCr level, median (IQR), mg/dL	0.95 (0.63–1.73)	0.60 (0.41–0.93)[a]
Concurrent nephrotoxins, No. (%)		
Loop diuretics,	18 (58)	26 (66.6)
Aminoglycosides	11 (35.5)	6 (15.4)
Contrast dye	10 (32.2)	14 (35.9)
Vancomycin	2 (6.4)	9 (23)
≥1 nephrotoxin	29 (93.5)	34 (87.2)
≥2 nephrotoxin	15 (48.4)	15 (38.4)
≥3 nephrotoxin	3 (9.7)	6 (15.4)
Concurrent ascorbic acid, No. (%)	13 (41.9)	30 (76.9)[a]

Abbreviations: ABW, actual body weight; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; CMS, colistimethate sodium; CrCl, creatinine clearance; IBW, ideal body weight; ICU, intensive care unit; IQR, interquartile range; MIU, million international units; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment.

[a] $P < .05$ for comparison with AKI group.

[b] $P < .05$ for comparison with CMS dose administered before AKI onset in the AKI group.

between colistin dose and renal toxicity. Colistin cumulative dose was defined as the sum of daily doses until the outcome (ie, development of AKI or end of colistin course).

Statistical Analysis

Data are expressed as medians and interquartile ranges (IQRs) or as numbers and percentages. Continuous data were compared using the Mann–Whitney *U* test. Categorical data were compared using Pearson χ^2 analysis or Fisher exact test when criteria for χ^2 application were not satisfied. A Cox proportional hazards analysis based on cumulative dose of colistin was performed to estimate the relative hazards of AKI. The assumption of proportionality was assessed by Kaplan–Meier profile for each predictor. The end of colistin therapy and patient death were the censoring events in the model. Variables were checked for confounding and collinearity. Covariates that met statistical criteria ($P < .05$) at univariate analysis and had biological plausibility for affecting the outcome were retained in the final model. The probabilities of AKI in subgroups (according to the findings of the proportional hazard model) were computed using the Kaplan–Meier method and were compared using the log-rank test. In all comparisons, differences were considered statistically significant at $P < .05$. Data were analyzed using SPSS software for Windows (version 16.0; SPSS).

RESULTS

Of 82 patients who received colistin for severe sepsis or septic shock caused by XDR gram-negative bacteria, 12 patients were excluded (9 receiving RRT at baseline and 3 who received colistin therapy for <72 hours); therefore, 70 patients were considered for analysis. Their median age was 64 (IQR, 48.5–75.2) years, and 62.8% were males. The median Charlson index was 2 (IQR, 0–4). The main comorbid conditions were arterial hypertension (42.8%), chronic heart failure (42.8%), obesity (40%), diabetes (24.3%), and chronic kidney disease (11.4%). The median APACHE II score was 21 (IQR, 16–25), and the median SOFA score, 8 (IQR, 5–10). Septic shock occurred in 54.3% of patients. Patients were treated for ventilator-associated pneumonia (52.8%), bloodstream infections (41.4%), and urinary tract infections (5.7%) due to XDR *Acinetobacter baumannii* (54.3%), *Klebsiella pneumoniae* (37.1%) and *Pseudomonas aeruginosa* (8.6%). The colistin MIC_{50} and MIC_{90} (ie, the MIC values which inhibited 50% and 90% of the isolates of each species tested) were 0.50 and 2 (range, 0.125–3) mg/L for *A. baumannii*, 1 and 1.5 (0.125–8) mg/L for *K. pneumoniae*, and 2 and 2 (1.5–3) mg/L for *P. aeruginosa*.

Colistin was administered for a median (IQR) 14 (11–18) days at a median (IQR) daily dose of 9 (5.87–11.1) MIU. A maximum daily dose of 10–12 MIU was administered to 22 patients (31.4%) for ≥2 consecutive days. Specifically, 12 MIU were administered to 19 patients, 11 MIU to 2, and 10 MIU to 1. In 61 patients, colistin was administered as combination therapy with rifampin (40%) and/or carbapenems (38.6%) and/or aminoglycosides (28%). Baseline renal impairment was present in 25.7% of patients. Nephrotoxin exposure was observed in 63 patients. The most frequently used agents were loop diuretics (70%), contrast dye (38%), aminoglycosides (27%), and vancomycin (17.4%). Nonsteroidal anti-inflammatory drugs, amphotericin B, and acyclovir were not administered. Low-dose hydrocortisone was administered in 42.8% of patients. Adjuvant ascorbic acid was given to 61.4%, administered at a twice-daily dose of 3 (2–4)g. Clinical resolution rate of infections was 77%. Six patients died.

AKI occurred in 31 patients (44.3%), graded as stages 1 (42%), 2 (29%), and 3 (29%) according to AKIN criteria, with a median (IQR) onset time of 5 (3–14) days after the beginning of colistin therapy. In 19 patients (61%), AKI developed within 7 days after the start of colistin treatment. In 20 patients (64.5%), renal recovery occurred a median (IQR) of 10.5 (8–13) days after AKI onset; in 8 patients, SCr levels were still higher than baseline levels 2 weeks after the end of colistin therapy; and 3 patients died. No patient required RRT or colistin discontinuation.

In univariate analysis, age, APACHE II score and SOFA score were associated with AKI (Table 1). The use of inhaled colistin was evenly distributed between patients with AKI and those without AKI (25.8% vs 24.6%, respectively). Compared with patients without AKI, those with AKI received lower cumulative and daily doses of intravenous colistin (Table 1). A maximum daily dose of 10–12 MIU was administered to 4 patients (12.9%) with AKI and 18 (46%) without AKI ($P = .003$).

Table 2. Cox Proportional Hazard Regression Model for Acute Kidney Injury Risk Based on Cumulative Colistin Dose

Variable[a]	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age	1.04 (1.01–1.06)	.003	1.03 (1.0–1.05)	.03
Baseline renal impairment	5.06 (2.4–10.6)	<.001	4.15 (1.9–9.2)	<.001
SOFA score	1.12 (1.01–1.24)	.03	1.09 (.9–1.3)	.19
Adjuvant ascorbic acid	0.26 (.12–.56)	<.001	0.27 (.13–.57)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

[a] The Acute Physiology and Chronic Health Evaluation (APACHE) II score at intensive care unit admission (crude HR, 1.07; 95% CI, 1.02–1.13; $P = .04$) was not included in the final multivariate model owing to some overlap with SOFA score, which better reflects the severity of sepsis at the beginning of colistin therapy. Replacing the SOFA score with the APACHE II score did not significantly change the results.

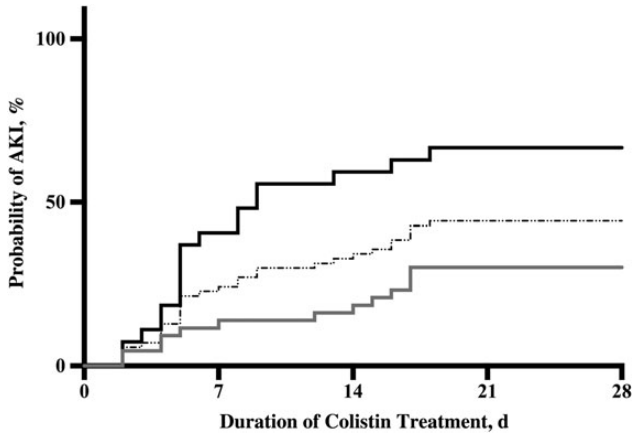

Figure 1. Time to development of acute kidney injury (AKI) during colistin exposure in the whole cohort, in patients who received ascorbic acid and in those who did not. Solid black line represents patients who received colistin only; dashed line, whole cohort; solid gray line, patients who received colistin plus ascorbic acid.

Patients with AKI had lower CrCl rates and were more frequently affected by renal impairment at baseline than those without AKI (Table 1). Coadministered nephrotoxic agents, concurrent exposure to multiple nephrotoxins (Table 1), and rifampin administration (32.2% of patients with AKI vs 46% of patients without AKI) did not differ between groups. Finally, patients who developed AKI were less frequently coadministered ascorbic acid (Table 1). In multivariate analysis, adjuvant therapy with ascorbic acid was found to have a strong protective role against AKI, whereas baseline renal impairment and age were the only independent predictors of AKI (overall model fit: $\chi^2 = 36.3$; $P < .001$; Table 2). The comparison of probabilities of AKI according to ascorbic acid adjuvant therapy, identified using a Cox regression model, showed that AKI risk increased earlier and was higher in patients who did not receive adjuvant ascorbic acid during colistin therapy (log-rank [Mantel–Cox] test, $\chi^2 = 20.16$, $P < .001$; Figure 1).

DISCUSSION

In patient with severe sepsis or septic shock receiving colistin according to a modified PK/PD-driven dosing strategy [2] AKI had an incidence rate of 44%, which well fits with the rates of 31%–45% reported in similar settings [3, 12, 13]. Consistently with previous studies, AKI occurred in 60% of cases within the first week of therapy [3, 6, 9, 21], was of mild to moderate severity, never required colistin discontinuation or RRT [3, 7, 9, 12, 22], and subsided in 64% of patients [3, 6], 10 days after its onset. Baseline renal impairment and older age predicted AKI occurrence, whereas coadministration of ascorbic acid markedly reduced AKI risk.

In the past 10 years, several promoters of colistin-related AKI have been found, but renal-protective factors have not been identified. The most frequently reported AKI promoters are advanced age [8, 10, 21–24], comorbid conditions [7, 21], preexisting impaired renal function [12, 24], severity of illness [13], nephrotoxic agents [6, 12, 23, 25], exposure to multiple nephrotoxins [3, 7, 8, 12], colistin daily dose [3, 9, 10, 26] and duration of therapy [5, 10].

In our study, renal impairment at the beginning of colistin therapy and older age were confirmed as independent promoters of AKI. Although AKI is considered a major limiting factor for adequate colistin exposure in critically ill patients [3, 9, 10], no relationship between colistin daily dose and AKI was found, as reported elsewhere [7, 8, 12, 13, 21]. For safety concerns, doses in our cohort were both targeted to a fixed colistin steady-state concentration of 2.5 mg/L [2] (independently on isolates colistin MIC) and capped at 9 MIU (270 mg CBA) and 12 MIU (360 mg CBA) in normal and augmented renal clearance conditions, respectively. This cap on the upper end of dosing may have biased the data toward colistin underexposure and might account for the lack of effect of administered dose on AKI occurrence. Moreover, when AKIN criteria were met, patients had already been dosed more conservatively according to the protocol, owing to the impending AKI or to the higher rate of baseline renal impairment.

Notably, however, renal overexposure and toxicity may have occurred. In patients with renal impairment, less CMS is renally excreted, thus exposing kidneys to a high colistin load [2, 27]. Consistent with previous data [12, 24], we found that a poor baseline renal function increased AKI risk by 4-fold. High peak and trough colistin plasma levels at steady state have been recently found in patients with baseline renal impairment [7], in spite of dose titration according to renal function. Moreover, trough level has been shown to independently predict nephrotoxicity, at a cutoff value of 2.42 mg/L [7]. Recently, colistin daily dose has been found to predict AKI only in patients with baseline renal impairment, at 3 mg CBA/kg or more [28], very close to the dosage of 3.2 mg CBA/kg/d administered in patients with baseline renal impairment before AKI onset in our study (data not shown). Therefore, it is likely that when recruitable renal reserve is very low, a PK/PD-driven dosing approach [2] may not be able to avoid undue renal exposure to colistin and should be guided by therapeutic drug monitoring.

Interestingly, in spite of colistin MIC values for the XDR isolates and severity of sepsis, our conservative dosing approach yielded a clinical resolution rate of nearly 80%, as reported in other settings [7, 25]. We cannot exclude the possibility that the use of combination therapy in almost all patients may have fostered this success rate.

So far, no factor able to reduce colistin-related AKI has been identified. Strikingly, our study showed that ascorbic acid was a strong nephroprotective agent, regardless of patient

age, preexisting renal impairment, and severity of sepsis. Although the pathogenesis of colistin-induced renal damage has not been yet fully elucidated, experimental study findings show oxidative damage and apoptotic injury as key underlying mechanisms of acute tubular necrosis [29–33] and are in agreement about the beneficial effect of anti-oxidant agents [29, 30, 34]. In a rat model of colistin-induced kidney injury, coadministered dose regimens of ascorbic acid equivalent to 2 g/d in humans for 7 days prevented renal tubular cells apoptosis and necrosis by free radical scavenging [35].

Our data are consistent with these preclinical findings. The chance of developing AKI for a patient receiving adjuvant ascorbic acid at a daily dose of 3 (2–4) g was 4 times lower than in a patient who did not receive ascorbic acid. Moreover, patients were at risk of AKI developing later, compared with those not receiving ascorbic acid. Critically ill septic patients have subnormal ascorbic acid plasma levels [36, 37], and daily intravenous administration of up to 3–6 g is needed to normalize plasma levels [38]. Although not graded in the recent Surviving Sepsis Campaign guidelines [39], in severe sepsis ascorbic acid administration has been associated with the prevention of new organ failures, by mitigating the microcirculatory impairment induced by oxidative injury [37, 38]. Therefore, our findings could be explained by a double kidney-protective effect toward both colistin-induced and septic renal damage. Interestingly, however, after we controlled for the severity of sepsis, ascorbic acid still turned out to be an independent nephroprotective agent. Recently, an interim analysis of a randomized, controlled study [40] did not find any benefit from using ascorbic acid with colistin in a small sample of moderately ill patients without confounding conditions likely to affect nephrotoxicity. Owing to the markedly different settings and colistin dosing, any comparison with our findings is precluded.

Some methodological limitations of our study must be acknowledged. First, because we did not directly monitor drug exposure with therapeutic drug monitoring, we did not evaluate the association between colistin plasma levels and AKI. Moreover, the nephrotoxicity of other agents beside colistin might have not been fully explored, leading to an underestimation of their role in colistin-related AKI. Finally, a conversion factor of 30 000, instead of 33 000, for conversion from milligrams of CBA of the Garonzik et al equation [2] to international units, was used, although with minor effect on doses.

Despite these limitations, our study includes methodological features that strengthen its findings. We evaluated a homogeneous population of severely ill septic patients who had a wide range of renal functioning and were receiving colistin at daily doses supported by current knowledge [2], and we defined AKI according to the most recent recommendations [4].

In conclusion, our observational study shows for the first time that ascorbic acid may be a promising nephroprotective agent in severely ill patients receiving colistin according to a PK/PD-driven dosing approach; a randomized, controlled trial is warranted. Moreover, AKI development should be expected in patients who are older or have baseline renal impairment. Therefore, both coadministration of ascorbic acid and assessment of age and renal function at the beginning of therapy could help physicians balance the need for reaching optimal dosing with the risk of AKI in each individual patient. It is hoped that both routine therapeutic drug monitoring and monitoring of renal biomarkers will prompt clinicians to adapt colistin dosage in a timely manner, thus avoiding renal overexposure.

Notes

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Potential conflict of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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