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Colistin nephrotoxicity increases with age

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Abstract

Background: Colistin (COL) has become the backbone of the treatment of infections due to extensively drug-resistant (XDR) Gram-negative bacteria. The most common restriction to its use is acute kidney injury (AKI). *Methods:* We conducted a retrospective cohort study to evaluate risk factors for new-onset AKI in patients receiving COL. The cohort consisted of 198 adults admitted to 9 referral hospitals between January 2010 and October 2012 and treated with intravenous COL for ≥ 72 h. Patients with no pre-existing kidney dysfunction were compared in terms of risk factors and outcomes of AKI graded according to the RIFLE criteria. Logistic regression analysis was used to identify associated risk factors. *Results:* A total of 198 patients met the inclusion criteria, of whom 167 had no pre-existing kidney dysfunction; the mean patient age was 58.77 ($\pm$ 18.98) y. Bloodstream infections (34.8%) and ventilator-associated pneumonia (32.3%) were the 2 most common indications for COL use. New-onset AKI developed in 46.1% of the patients, graded as risk (10%), injury (15%), and failure (21%). Patients with high Charlson co-morbidity index (CCI) scores ($p = 0.001$) and comparatively low initial glomerular filtration rate (GFR) estimations ($p < 0.001$) were more likely to develop AKI, but older age ($p = 0.001$; odds ratio 5.199, 95% confidence interval 2.684–10.072) was the major predictor in the multivariate analysis. In-hospital recovery from AKI occurred in 58.1%, within a median of 7 days. *Conclusions:* COL-induced nephrotoxicity occurred significantly more often in patients older than 60 y of age and was related to low initial GFR estimations and high CCI scores, which were basically determined by age.

Keywords: *Colistin, nephrotoxicity, age*

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Introduction

Colistin (COL) has become the backbone of the treatment of infections due to multidrug-resistant (MDR) Gram-negative bacteria, particularly extensively drug-resistant (XDR) and COL-only susceptible strains. Given the recent rates of carbapenem resistance among Acinetobacter spp. (67.6–70.4%) and Pseudomonas spp. (26.3–35.8%) in the training and university hospitals throughout Turkey, COL is likely to be used increasingly more often [1]. In most clinical settings, the most common restriction to its use is nephrotoxicity due to tubular damage [2]. Early experience with COL revealed a high incidence of toxicity and it was widely abandoned in the 1970s because of adverse effects. In the late 1990s, with the stepwise trend towards multiple drug resistance in Gram-negative bacteria and severe infections with high mortality rates due to these organisms, clinicians were forced to resort to salvage therapy with COL. The high rates of acute kidney injury (AKI) in early cases were probably due to the lack of true pharmacokinetic/pharmacodynamic data, the use of high doses, and inadequate facilities for kidney replacement therapy. However, recent data from published reports do not corroborate this finding [3]. Explanations for the lower overall toxicity today include fewer chemical impurities in colistimethate sodium, better intensive care unit (ICU) monitoring, and avoidance of co-administration of other nephrotoxic drugs [4].

Although there are many studies reporting COL nephrotoxicity at various rates, studies specifically focusing on the features and risk factors for COL-induced AKI are scarce. In this study we aimed to investigate the outcomes of COL use, establish the risk factors contributing to COL-related nephrotoxicity, and provide evidence for more beneficial use of COL to avoid renal dysfunction.

Patients and methods

Study design

A multicenter retrospective cohort study of adults receiving intravenous COL was conducted at 9 referral hospitals between January 2010 and October 2012. Pharmacy-generated reports and medical records were used to identify patients who had received intravenous COL during the study period.

The following patients were excluded: (1) those who had received COL $<$ 72 h, (2) those who had received only inhaled COL, (3) those who were lacking at least 3 (initial, highest, and end of treatment) consecutive measurements of serum creatinine (S_{CR}), and (4) those who were under 18 y of age or pregnant.

If a patient had received multiple courses of COL, only the first was considered in the analysis. The whole cohort was divided into 3 groups: (1) patients with normal baseline S_{CR} with no increase in S_{CR} during COL treatment, or a small rise lower than 1.5-fold; (2) patients with normal baseline S_{CR} and an at least 1.5-fold increase during COL treatment; (3) patients with pre-existing kidney dysfunction defined as a baseline $S_{CR} > 1.3$ mg/dl for females and > 1.5 mg/dl for males.

Patients with and without AKI due to COL use were compared in terms of risk factors and outcomes. AKI was graded according to the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) [5]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation formula was used to estimate the initial glomerular filtration rates (GFRs) of the patients [6]. Estimated initial GFR values were not used for the classification of the patients in order not to cause a deviation from the daily clinical practice based on initial S_{CR} levels. Patients with previously defined underlying kidney injury with either chronic renal failure (CRF) or acute renal failure (ARF) were not included in the analyses for the primary and secondary outcomes. They were evaluated only in the total descriptive analysis and subgroup analysis in terms of other outcomes.

Data collection

A standardized case form was used to record patient characteristics, including age, gender, weight, underlying co-morbidities (evaluated by Charlson co-morbidity index; CCI), acute physical condition (evaluated by Acute Physiology and Chronic Health Evaluation II score; APACHE II), site and type of infection, causative bacteria and in vitro susceptibility, daily doses and duration of COL therapy, cumulative dose of COL (mg/kg; daily dose per kg of body weight $\times$ duration of treatment), co-administered antibiotics, concomitant nephrotoxic agents (at the time of data collection and at least since the last week for drugs and once in the last week for radio-contrast agent; agents included aminoglycosides, vancomycin, acyclovir, amphotericin B, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II blockers (ATBs), intravenous radio-contrast agents), serum albumin levels, serial serum creatinine levels, and clinical and microbiological responses to therapy [7,8]. The primary outcome was the development of AKI during COL treatment. Secondary outcomes were the risk factors for AKI, features of AKI, and outcomes of COL use including mortality.

Definitions

RIFLE criteria are defined as follows: risk (R), increased creatinine level $\times 1.5$ or GFR decrease $>25\%$; injury (I), increased creatinine level $\times 2$ or GFR decrease $>50\%$; failure (F), increased creatinine level $\times 3$, GFR decrease $>75\%$, or S_{CR} level >4 mg/dl; loss (L), persistent acute renal failure or complete loss of function for >4 weeks; end-stage kidney disease (ESKD) (E), ESKD for >3 months. Renal recovery was defined as the return of decreased kidney function to pre-AKI baseline levels and was assessed during the subject's hospitalization. Hospital infections were defined according to the definitions of the US Centers for Disease Control and Prevention (CDC). MDR was defined as non-susceptibility to at least 1 agent in 3 or more antimicrobial categories. XDR was defined as non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only COL and tigecycline) [9].

Colistin administration

The COL used in this study was Coli-Mycin Parenteral (Kocak Farma, Istanbul, Turkey). It contains 150 mg of 'COL base activity', equivalent to 360 mg (or 4.5×10^6 IU) of colistimethate sodium per vial. It was dissolved in 100 ml sterile saline and was given over 30 min. The administration of COL was based on the results of in vitro antimicrobial susceptibility tests (targeted) or a high clinical suspicion of infections due to COL-only susceptible pathogens (empirical), with the approval of the infectious diseases consultant, according to national regulations. The dosage of intravenous (IV) COL recommended by the manufacturer is 2.5–5.0 mg/kg/day for patients with normal renal function. In patients with moderate-to-severe renal impairment (creatinine clearance rate <50 ml/min), dosing adjustments were made in accordance with the manufacturer's instructions. None of the patients received a loading dose of COL. Administration of a loading dose as suggested by recent studies had not been implemented during the study period [10]. Treatment duration was determined on the basis of the clinical response during follow-up.

Statistical analyses

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. In general comparisons, categorical variables were compared by Chi-square test or Fisher's exact test, and continuous variables were tested with the Student's *t*-test or one-way analysis of variance (ANOVA), as appropriate. Significant variables in the univariate analysis were tested by Spearman's logistic regression in order to determine the independent risk factors for COL-induced AKI. A receiver operating characteristic (ROC) curve was drawn to determine the threshold value of the variable that most likely contributes to AKI. For all analyses, a 2-sided *p*-value of <0.05 was considered to be statistically significant.

Ethical approval

This study was approved by the Institutional Review Board of Istanbul University Cerrahpasa Medical Faculty (Registration date and number 04.12.2012/A-23); the need for informed consent was waived due to the retrospective design of this study. The confidentiality of all data collected was maintained.

Results

Patient data

A total of 198 patients from 9 referral centres were included in the study. Four patients were excluded; 3 because they received only inhaled COL and 1 because of age below 18 y. One hundred and twenty-one patients were male (61.1%) and the mean patient age was 58.77 ($\pm$ 18.98) y.

One hundred and thirty-eight patients (69.7%) were hospitalized in ICUs, 34 (17.2%) in internal medicine units, and 26 (13.1%) in surgical units. Thirty-one patients had pre-existing kidney dysfunction; 27 had CRF and 4 had ARF. At least 1 co-morbidity was present in 75.4% of patients; 44 (22.2%) had cardiovascular diseases, 26 had hypertension, 37 (18.7%) had diabetes mellitus, 33 (16.7%) had neurological diseases, 29 (10.1%) had solid tumours, 23 (11.6%) had pulmonary diseases, 21 (10.6%) had haematological malignancies, 20 (10.1%) were immunosuppressed, and 17 (8.6%) had major trauma or burns.

The majority of patients had bloodstream infections (BSIs; 34.8%; primary bacteraemia in 50, secondary bacteraemia in 12, and central line-associated BSI in 7), ventilator-associated pneumonia (VAP; 32.3%), nosocomial pneumonia (14.6%), complicated surgical site infection (8.5%), intra-abdominal infection (2.5%), nosocomial meningitis (1%), nosocomial urinary tract infection (UTI; 0.5%), and mediastinitis (0.5%). The causative bacteria were Acinetobacter baumannii (74.2%), Pseudomonas aeruginosa (10.1%), Klebsiella pneumoniae (6.1%), Escherichia coli (1.0%), and Gram-negative bacilli (3.5%). Ten cases (5.1%) were treated empirically.

Thirteen patients (6.5%) received COL monotherapy and 185 (93.5%) received combination therapy with other antibiotics such as carbapenems (45%), aminoglycosides (5.5%), tigecycline (8%), sulbactam (19.7%), cefoperazone–sulbactam (15.5%), piperacillin–tazobactam (4.1%), quinolones (6%), ceftazidime (2.4%), and cefepime (1.8%). Thirty-four patients received triple combinations where COL was most commonly combined with carbapenem plus sulbactam (35.3%). Glycopeptides were the most common accompanying antibiotics used in 37 (18.7%) of the cases, while 132 (66.2%) did not receive additional antimicrobial drugs.

Inhaled COL was used in 29 (45.3%) patients with VAP, in 3 (10.3%) patients with nosocomial pneumonia, and in 32 (34.4%) patients with respiratory infections due to XDR Gram-negative rods.

The initial daily COL dose was 300 mg/day in 140 (70.7%), 200 mg/day in 12 (6.1%), 450 mg/day in 7 (3.5%), 240 mg/day in 5 (2.5%), 400 mg/day in 3 (1.5%), 150 mg/day in 23 (11.6%), 150 mg every 48 h in 4 (2%), 150 mg every 36 h in 3 (1.5%), and 100 mg/day in 1 (0.5%) of the cases ($n = 198$). The latter 4 doses were preferred in patients with chronic kidney dysfunction ($n = 31$). Initial COL doses were not modified during treatment in 163 (82.3%) patients. Dose modification was performed in 35 (17.7%) patients due to AKI. The most common dose modification was switching to a once-daily dose of 150 mg IV. None of the patients had bacteria that developed resistance to COL during treatment and none received excessive doses of COL. Reasons for COL cessation are shown in Table I.

Toxicities

Nephrotoxicity. A total of 77 (46.1%) patients with normal baseline kidney function developed AKI during COL use and met the RIFLE criteria at the time of their peak serum creatinine (S_{CR}) level. AKI was consequently graded as risk in 10%, injury in 15%, and failure in 21%. Risk factors for AKI are shown together with the basic demographic characteristics of the patients in Table I. In the univariate analysis, mean age ($p = 0.001$), mean CCI ($p = 0.001$), and concomitant use of ACE inhibitors ($p = 0.003$) were significantly higher while mean initial GFR estimations were significantly lower in those who developed AKI. In the logistic regression analysis, old age was the significant risk factor for AKI during COL treatment. ROC curve analysis showed that patients over 60 y of age had a significantly higher risk of AKI (70.1%) when compared to those under 60 y of age (31.1%) ($p = 0.001$; odds ratio 5.199, 95% confidence interval 2.684–10.072). AKI of any grade resolved within the in-hospital period in 58.1% of patients, mostly within 7 days (median 6.5 days, range 3–105 days) (Table III).

Neurotoxicity. Neurotoxicity was observed in 1 patient (0.5%) as facial numbness, which resolved 5 days after discontinuation.

Mortality

Overall mortality was 36.3%. There was no significant difference between the groups with and without AKI in terms of 28-day mortality (41.6% vs. 28.9%, $p = 0.086$). The proportion of patients who died due to severe disease before COL cessation was higher in those who developed AKI (33.3% vs. 20%, $p = 0.052$). The 28-day mortality rate was 45% in patients with pre-existing kidney dysfunction (Table IV).

Discussion

COL-related nephrotoxicity remains a significant problem. This retrospective cohort study showed a high AKI rate of 46% in patients with no pre-existing kidney dysfunction who received intravenous COL. Higher CCIs, lower initial estimated GFR levels (despite similar initial S_{CR} levels), and the use of concomitant ACE inhibitors were found to be risk factors in the univariate analysis. The first 2 factors were basically determined by higher age, which was the only significant risk factor in the logistic regression, particularly when over 60 y.

A number of studies designed to assess nephrotoxicity have recently been published in which the rate has ranged from 6% to 60% [11–20]. Differences in the characteristics and risk factors of the subjects and the burden of COL exposure account in part for this variation. However, it is basically related to the lack of common criteria to define kidney injury [21]. The introduction of the RIFLE criteria provided a definition standard for studies assessing this outcome. A comparison of the present study with some recent reports adopting the same criteria (Table V) revealed a higher proportion of patients with 'failure' (21%). Despite higher rates of 'failure', only 4 (2.4%) patients required renal replacement therapy (RRT) in our cohort and 15 (7.7%) patients discontinued COL. AKI was reversible, was not severe, did not cause discontinuation of COL in most cases, mostly subsided rapidly, and no case required long-term dialysis in our study, in concordance with some previous reports [14].

Underlying kidney dysfunction is the major determinant of drug-induced AKI. Based on the data revealing high frequencies (> 60%) of COL-induced nephrotoxicity in patients with previous renal dysfunction, the outcomes of this subset of our cohort are shown separately (Table IV).

Table I. Comparison of characteristics of patients who developed AKI ($n = 77$) and those who did not develop AKI ($n = 90$) during colistin use; univariate analyses.

Risk factor	No AKI ($n = 90$)	AKI ($n = 77$)	p-Value	OR (95% CI)
Mean age (y)	48.72	66.71	0.001	5.199 (2.684–10.072)
Male (%)	63.3	57.1	0.432	
Mean CCI score	2.33	3.88	0.001	
Initial GFR (ml/min)[a], mean ± SD	108.91 ± 26.258	91.77 ± 22.522	< 0.001	11.4 (9.198–25.095)
Hypertension, *n* (%)	13 (14.4)	13 (16.9)	0.826	
Diabetes mellitus, *n* (%)	13 (14.4)	16 (20.8)	0.383	
Malignancy, *n* (%)	14 (15.6)	11 (14.3)	0.991	
Mean BMI (kg/m^2)	37	24	0.375	
Mean total hospital stay (days)	58.14	56.44	0.807	
Mean ICU stay (days)	53.8	45	0.266	
APACHE II score[b], mean ± SD ($n = 120$)	17.2 ± 8.1	18.2 ± 7.1	0.488	
Initial serum creatinine (mg/dl)	0.627	0.674	0.341	
Highest serum creatinine (mg/dl)	0.751	2.095	0.001	
End-treatment serum creatinine (mg/dl)	0.630	1.790	0.001	
Initial albumin (mg/dl)	2.641	2.545	0.266	
End-treatment albumin (mg/dl)	2.792	2.595	0.144	
Mean hospital stay before COL use (days)	27.88	27.55	0.066	
Mean total COL dose (mg)	4310.44	3526.71	0.145	
Mean duration of COL use (days)	13.74	13.47	0.205	
Concomitant medications[c], *n* (%)				
Methotrexate	0 (0.00%)	1 (1.30%)	0.561	
AMB[d]	1 (1.10%)	2 (2.60%)	0.595	
Acyclovir[d]	7 (7.80%)	2 (2.60%)	0.18	
NSAIDs[d]	3 (3.30%)	2 (2.60%)	1.000	
ACE inhibitors[d]	0 (0.00%)	7 (9.10%)	0.003	
VA[d]	8 (8.90%)	4 (5.20%)	0.535	
Aminoglycoside[d]	6 (6.70%)	5 (6.50%)	1.000	
IV Contrast	16 (17.70%)	9 (12%)	0.475	
Co-administered antimicrobials				
Carbapenem	45 (50%)	27 (35.10%)	0.052	
Tigecycline	4 (4.40%)	10 (13%)	0.088	
Sulbactam	15 (16.70%)	18 (23.40%)	0.373	
Cefoperazone–sulbactam	19 (21.10%)	7 (9.10%)	0.055	
Ceftazidime	2 (2.20%)	2 (2.60%)	1.000	
Cefepime	1 (1.10%)	2 (2.60%)	0.595	
Piperacillin–tazobactam	3 (3.30%)	4 (5.20%)	0.705	
Quinolone	6 (6.70%)	4 (5.20%)	0.754	
Rifampicin	0 (0.00%)	1 (1.30%)	0.461	

AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; CCI, Charlson co-morbidity index; GFR, glomerular filtration rate; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; COL, colistin; AMB, classic or liposomal amphotericin B; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme; IV, intravenous; VA, Vancomycin.
[a]Glomerular filtration rate was calculated using the CKD-EPI Creatinine Equation (2009).
[b]APACHE II scores were calculated only for ICU patients.
[c]Within the last 7 days.
[d]Use for ≥ 3 days.

Table II. Reasons for colistin cessation ($n = 193$)[a].

Reason	*n*	%
Clinical recovery	97	50.3
Death	64	33.2
Treatment failure	13	6.7
Nephrotoxicity	15	7.7
Switch to other agent based on culture results	4	2.1
Other reasons	2	1.0
Total	193	100.0

[a]Data unavailable for 5 cases.

The dose-related nature of COL-induced toxicity is well defined in the literature [16,17,20,22]. Sorlí et al. have recently shown that COL-induced AKI is significantly correlated with the plasma minimum concentration of COL on day 7 of treatment [23]. In our study we could not establish the correlation between daily or cumulative doses of COL and renal damage. The mean body mass index (BMI), as a recently defined risk factor for over-dosing COL, was also similar in the 2 groups [24].

Table III. Features of AKI during colistin use ($n = 167$).

Feature	*n* (%)
No toxicity	90 (53.9%)
Risk (S_{CR}X1,5)	17 (10.1%)
Injury (S_{CR}X2)	25 (15%)
Failure (S_{CR}X3)	35 (21%)
Loss (persistent ARF > 4 weeks)	0
ESKD	0
COL dose reduction due to AKI	27 (16.1%)
Median day of dose reduction (range)	7 (2–24 days)
Cessation of COL due to AKI	12 (7.1%)
Median day of cessation (range)	9 (4–17 days)
Requirement of temporary RRT due to AKI	4 (2.4%)
In-hospital recovery of AKI ($n = 74$)	43 (58.1%)
Median day of recovery (range) ($n = 26$)	6.5 (3–105 days)

AKI, acute kidney injury; S_{CR}, serum creatinine; ARF, acute renal failure; ESKD, end-stage kidney disease; COL, colistin; RRT, renal replacement therapy.

Several other risk factors are defined for the development of AKI during COL use in different studies (Table V). Age has been documented as a risk factor in some earlier and recent studies [17,20,26]. The effect of age probably derives from its major contribution to the estimation of baseline kidney function and co-morbidity scores. This hypothesis is supported by a prospective cohort study where COL use showed no adverse effect on kidney function in 55 patients treated for Pseudomonas or Acinetobacter infections with a relatively low mean age of 40 ± 16 y [28].

Among patients who developed AKI, 7 (9.1%) had records of concomitant ACE inhibitor use, while no patient without AKI had received concomitant ACE inhibitors or ATBs. When ACE inhibitor receivers and non-receivers were compared, mean baseline GFR rates according to the CKD-EPI equation 2009 were similar (80.42 vs 78.76 ml/min $p = 0.98$). Although not significant in the further analysis, this effect should be noted for concomitant users of COL and ACE inhibitors. ACE inhibitors and ATBs are preferred for their nephroprotective and cardioprotective effects in the treatment of hypertension. However, apart from the decrease in the systemic blood pressure as a consequence of their relatively more potent vasodilatory effect on the efferent arterioles compared to the afferents, they possibly interfere with the kidneys' ability to autoregulate glomerular pressure and decrease GFR by reducing the intraglomerular pressure [29]. This causes a predisposition to renal toxicity with a similar mechanism that is observed in patients with dehydration or hypotension for any reason. Adequate hydration is one of the most important components of patient follow-up to maintain renal perfusion and avoid drug-induced renal impairment. The concomitant use of other nephrotoxic agents including aminoglycosides and vancomycin did not correlate to an increased risk of AKI in our cohort.

Table IV. Outcomes of colistin use in patients with pre-existing chronic renal dysfunction ($n = 31$).

Parameter	*n* (%)
Age (y), mean ± SD	70.77 ± 12.42
Male	19 (61.3%)
Mean total COL dose (mg)	1864.84
Clinical recovery with COL treatment ($n = 30$)	10 (33.3%)
Clinical failure with COL treatment ($n = 30$)	2 (6.7%)
Mean initial serum creatinine (mg/dl)	2.79
Mean highest serum creatinine (mg/dl)	3.48
Mean end-treatment serum creatinine (mg/dl)	2.65
Median initial serum urea (mg/dl)	56
Median highest serum urea (mg/dl)	113
Median end-treatment serum urea (mg/dl)	99
Mean initial albumin (mg/dl) ($n = 27$)	2.46
Mean end-treatment albumin (mg/dl) ($n = 28$)	2.34
Requirement of RRT during COL use	5 (16%)
COL cessation due to AKI ($n = 30$)	3 (10%)
28-day mortality ($n = 31$)	14 (45.2%)
Mortality during COL use ($n = 31$)	10 (32.3%)

SD, standard deviation; COL, colistin; RRT, renal replacement therapy; AKI, acute kidney injury.

COL was discontinued due to a rise in S_{CR} in 15 (7.7%) cases at a median 9 days (range 4–17 days) in our study cohort ($n = 198$). Some previous studies have reported similar rates [12,13,30]. The median time to nephrotoxicity was 7 days in our cohort, in contrast to the study by Collins et al., who reported a median time of 12 days in a cohort of 57 critically ill patients receiving COL with concomitant nephrotoxic antibiotics [26]. Early-onset (< 7 days) AKI has been associated with increased mortality during COL use [26].

In our study, AKI of any grade recovered in 58.1% of patients, mostly within 7 days (median 6.5 days, range 3–105 days). Given the mild and reversible features of nephrotoxicity, if data regarding those who recovered after discharge were available, the rate of recovery from AKI would be even higher. Along with being a major risk factor for AKI, old age did not change the rate or the duration of recovery in our cases. Recovery rates were not significantly different in those under or over 60 y of age (30/62 and 16/24 respectively; $p = 0.153$) or in non-users or users of ACE inhibitors (52.5% of non-users and 66.6% of users recovered; $p = 0.681$). Time to recovery was not significantly different ($p > 0.05$).

The main limitation of this study is its retrospective design, in which analysis of nephrotoxicity was limited even with the use of a standardized definition. Although hypertension and diabetes mellitus rates were not significantly different in the 2 groups, other causes of nephropathy (i.e. hydration status) could

Table V. Studies Assessing COL induced AKI According to RIFLE Criteria.

Studies in chronological order	Number of patients	AKI n, %	R	I	F	L	E	Predictors of COL induced AKI
Hartzell et al., CID 2009 [16]	66	30 (45%)	13 (20%)	10 (15%)	7 (11%)	0	0	1. Total COL dose 2. Duration of COL treatment
Kwon et al., IJAA 2010 [21]	71	38 (53.5%)	11 (15.4%)	10 (14%)	17 (23.9%)	0	0	1. Male sex 2.Concomitant use of calcineurin inhibitors 3. Hypoalbuminaemia 4. Hyperbilirubinaemia
DeRyke et al., AAC 2010 [17]	30	10 (33%)	3 (10%)	5 (16.6%)	2 (6.6%)	0	0	1. Excessive colistin dosing due to use of actual body weight in obese patients 2. Concomitant diuretic use 3. Concomitant use of vasopressors 4. Older Age
Pogue et al., CID 2011 [24]	126	54 (43%)	16 (13%)	21 (17%)	16 (13%)	0	0	1. COL dose of $\geq$5.0 mg/kg per day of ideal body weight 2. Concomitant use of rifampin 3. Receipt of $\geq$3 concomitant nephrotoxins
Doshi et al., Pharmacotherapy, 2011 [25]	49	15 (31%)	4 (8%)	7 (14%)	2 (4%)	1 (2%)	1 (2%)	1. Chronic kidney disease 2. Hypertension 3. Receipt of intravenous contrast material 4. Co-administration of $\geq$2 nephrotoxic agents
Collins et al., Pharmacotherapy 2013 [26]	174	84 (48%)	37 (21%)	20 (11%)	15 (9%)	11 (6%)	0	1. Age 2. Receipt of concomitant nephrotoxins
Rocco et al., Crit Care, 2013 [27]	147	57 (38.7%)	9 (6%)	13 (8.8%)	35 (23.8%)	0	0	1. Septic shock 2. High SAPS II score ($\geq$43)
Sorli et al, BMJ Infect Dis, 2013 [23]	102	48 (49%)	14 (13.7%)	23 (22.5%)	13 (12.7%)	0	0	1.Minimum plasma COL level on day 7 (C_{min}) 2. High Charlson score 3. Co-administration of $>$2 nephrotoxic drugs
Balkan et al. (present study)	167	77 (46.1%)	17 (10%)	25 (15%)	35 (21%)			1. Age 2. High Charlson score 3. Low initial GFR
TOTAL	830	365 (44%)	110 (13.2%)	111 (13.3%)	129 (15.5)	12 (1.4)	1 (0.1)	

not be thoroughly ruled out. Pharmacokinetic and pharmacodynamic parameters were not available for assessment and COL doses were not standardized. Despite these limitations, our study offers an insight into a variety of patients with a wide range of underlying diseases who received IV COL for severe infections, from 9 different centres across the most populated regions of the country.

In conclusion, nephrotoxicity during COL use occurs significantly more frequently after 60 y of age and is related to low initial GFR estimations and high CCI scores, which are basically determined by age.

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