TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1165-1172
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doi:10.3906/sag-1604-60

Risk factors for colistin-associated nephrotoxicity and mortality in critically ill patients

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Received: 13.04.2016 • **Accepted/Published Online:** 31.03.2017 • **Final Version:** 23.08.2017

Background/aim: Colistin is gaining popularity against multidrug-resistant bacteria. The primary concern with colistin is its nephrotoxicity (NT). The aim of this study was to evaluate the incidence and risk factors for NT and to evaluate the risk factors for mortality in the toxicity group.

Materials and methods: NT was defined according to the RIFLE criteria. Data of patients who did or did not develop NT were compared. Positive and negative predictive values, risk ratio, and correlation coefficients were calculated.

Results: NT was seen in 39 patients (70%). Hypoalbuminemia, old age, and the use of vasopressors (VPs) were associated with NT. The use of VPs had the highest positive predictive value, while age had the highest negative predictive value and risk ratio. The only variable that was associated with mortality in the toxicity group was VP use.

Conclusion: Aging, hypoalbuminemia, and the use of VPs were shown to be risk factors for NT, while the last of these was the only significant risk factor for mortality in the toxicity group.

Key words: Colistin, risk factors, nephrotoxicity, mortality

1. Introduction

Over the last few decades, there has been a marked increase in the incidence of nosocomial infections caused by multidrug-resistant gram-negative bacteria, particularly in critically ill patients (1). The shortage of new antibiotics that specifically target these pathogens has recently rekindled interest in colistin, a historical antimicrobial agent, discovered in 1949. The use of colistin declined from the early 1970s to the early 2000s, due to its frequent adverse effects, including a high incidence of nephrotoxicity (NT) (2,3).

It has been reported in many studies that NT was associated with a poor outcome and high mortality rates in critical patients (4–6). The reported incidence of NT varies from 0% to 60% (7–11). The wide range in colistin-associated acute kidney injury (AKI) may be attributed to inconsistency in how AKI was defined. Most of the earlier studies did not clearly define the NT. In several recent studies, NT was defined with specific criteria; however, varying definitions have complicated study comparisons (12–17). In 2004, the Acute Dialysis Quality Initiative Group published their consensus definition for AKI; the Risk, Injury, Failure, Loss, End stage renal disease (RIFLE) classification is based on the change in the glomerular filtration rate (GFR), serum creatinine levels, or urinary output. The RIFLE approach can detect AKI with high sensitivity and specificity (18). Studies assessing colistin-associated NT according to RIFLE are scarce in the literature (19). In this study, we aimed to determine the risk of renal damage according to the RIFLE criteria in critically ill patients in the intensive care unit and secondarily aimed to determine the predictive factors that facilitate the development of renal damage.

2. Materials and methods

2.1. Study design, setting, and patient population

After approval from the hospital ethics committee, a retrospective, cohort study was conducted in the 27-bed intensive care unit (ICU) of a tertiary care hospital (İzmir Tepecik Training and Research Hospital) in İzmir. Patients who received intravenous colistin between 1 January 2013 and 1 April 2014 were included in the study. Patients aged over 18 years and who received intravenous colistin for at least 72 h were included.

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Patients were excluded if they had been previously diagnosed with chronic renal disease, regardless of the need for hemodialysis. Patients with heart failure, liver disease, and malignancy were also excluded. If a patient met the inclusion criteria on multiple occasions, only the first qualifying episode was evaluated.

The product used in this study was colimycin (colistimethate sodium produced by Koçak Farma, Turkey) available as 150 mg of colistin base activity per vial. Colistimethate sodium dosage is regulated as 2.5–5 mg/kg (maximum 300 mg) in patients who do not have renal insufficiency. We therefore used 5 mg/kg colistin loading dose followed by two doses of 5 mg/kg (maximum 300 mg) in accordance with the infectious diseases physician's recommendations; subsequent dosages were adjusted according to the serum creatinine (Scr) levels.

The decision to use colistin was based on the recommendation of an infectious disease specialist and the results of susceptibility testing given resistance to all antibiotics apart from colistin.

2.2. Study variables, definitions, and measurements

The electronic medical records for the study patients were retrospectively reviewed using a standardized data collection form. The following baseline characteristics of the patients were collected from the medical records: age, sex, and the simplified acute physiology score (SAPS II). Causative microorganisms, coexistence of severe sepsis, and septic shock were recorded. Severe sepsis and septic shock were defined according to the Surviving Sepsis Guidelines (20). Concomitant use of other nephrotoxins (nephrotoxic antimicrobials, loop diuretics, intravenous dye, nonsteroidal antiinflammatory drugs (NSAID), angiotensin-converting-enzyme (ACE) inhibitors, and calcineurin inhibitors), use of vasopressors (VPs), serum albumin levels, and duration of colistin therapy were recorded. NT was determined by the RIFLE criteria. RIFLE has three severity classes, which were assessed by relative changes in either Scr or the GFR from a baseline value, or by a decrease in urine output at a predetermined time interval. The two outcome criteria were defined by the duration of the loss of kidney function, which was assessed at the 4th week (loss) and 3rd month (end-stage kidney disease) (Table 1).

If data were not available for assessing the GFR at the 4th week and 3rd month, due to patient death or discharge, only the acute degree of NT was considered. The need for renal replacement therapy was also recorded.

2.3. Statistical analysis

IBM SPSS version 22.0 (IBM Corp, Somers, NY, USA) was used for statistical analysis. Normality was assessed using the Kolmogorov–Smirnov test. Continuous normally distributed data, expressed as mean ± SD, were compared using an independent sample t-test. Nonnormally distributed data, expressed as median and interquartile range (IQR), were compared using the Mann–Whitney U-test. Categorical data are expressed as number (n) and percentage (%) of events and compared by the Pearson chi-square or the Fisher exact test. The data were analyzed at a confidence level of 95%. A P-value of less than 0.05 was considered statistically significant.

The receiver operating characteristic (ROC) curve was used to evaluate the cut-off values of the independent numerical variables with a P-value less than 0.05. The Youden's indices were calculated and the maximum Youden's index was used as the cut-off value in the ROC curve. Cut-off values for nephrotoxicity and mortality

Table 1. RIFLE criteria.

	GFR criteria	Urine output criteria
Risk	Increased S_{Cr} × 1.5 GFR decrease > 25%	<0.5 mL/kg/h × 6 h
Injury	Increased S_{Cr} × 2 GFR decrease > 50%	<0.5 mL/kg/h × 12 h
Failure	Increased S_{Cr} × 3, GFR decrease > 75% S_{Cr} ≥ 4 mg/dL with an acute rise > 0.5 mg/dL	< 0.3 ml/kg/h × 24 h, or anuria × 12 h
Loss	Persistent ARF or loss of function > 4 weeks	
ESRD	ESRD > 3 months	

GFR: Glomerular filtration rate,
S_{Cr}: Serum creatinine,
ARF: Acute renal failure,
ESRD: End stage renal disease

were separately analyzed. Area under the curve (AUC) values of 0.9–0.99, 0.8–0.89, 0.7–0.79, 0.6–0.69, and <0.6 were considered excellent, good, reasonable, poor, and failed discrimination, respectively.

According to the cut-off values cases were divided into two groups, high-risk group and low-risk group and a chi-squared test was performed subsequently. Prediction accuracy was evaluated using positive predicted value (PPV) and negative predicted value (NPV). Correlation coefficient (phi), relative risk (RR), and odds ratio (OR) were also calculated.

3. Results

Over the study period, 1089 patients were admitted to our ICU. Of these, 71 received colistin. In total, 71 patients were evaluated and 56 met all inclusion/exclusion criteria as 15 patients were excluded because 10 had chronic kidney disease and 5 received colistin for less than 72 h (Figure). SAPS II, baseline creatinine levels, and length of ICU stay were nonnormally distributed for NT. Skewness and kurtosis were 0.88 (SE = 0.39) and 1.14 (SE = 0.63) for SAPS II, 0.84 (SE = 0.32) and 0.95 (SE = 0.63) for creatinine levels, and 2.87 (SE = 0.32) and 10.44 (SE = 0.63) for ICU stay, respectively.

Assessing mortality in patients who developed NT, age, baseline creatinine levels, length of ICU stay, and time to NT were nonnormally distributed. Skewness and kurtosis were –1.048 (SE = 0.378) and 1.071 (SE = 0.741) for age, 0.83 (SE = 0.38) and 0.92 (SE = 0.74) for creatinine levels, 2.60 (SE = 0.38) and 8.16 (SE = 0.74) for ICU stay, and 1.33 (SE = 0.38) and 1.51 (SE = 0.74) for time to NT, respectively.

3.1. Descriptive data

Of the 56 patients, 29 were male (51.8%). The median (IQR) SAPS II score was 47.50 (42.25–60.00). The mean ± SD of age and albumin level was 64.09 ± 20.89 and 2.28 ± 0.49, respectively. In total, 38 (67.9%) were medical patients, 11 (19.6%) were admitted after surgery, and seven (12.5%) were trauma patients.

A. baumannii was the only detectable microorganism in 52 patients. Four patients, who had refractory fever and other evidence of infection, received colistin empirically. While the most frequent infection was ventilator-associated pneumonia (57.7%), bloodstream infections (25.0%), surgical site infections (15.4%), and urinary tract infections (1.9%) were also observed.

Severe sepsis and septic shock were seen in 18 patients. The mean ± SD duration of colistin therapy was 11.54 (±5.58) days. During the colistin therapy, nine patients were exposed to other nephrotoxic agents. Six patients received other nephrotoxic antibiotics. The most frequent concomitant use of nephrotoxic antibiotics was vancomycin in three patients. Two patients received aminoglycoside, and one patient received vancomycin and aminoglycoside in combination. Two patients were administered NSAIDs, while radiocontrast medium was given to one patient. Twenty patients required VP therapy.

3.2. Outcome data

Thirty-nine (70%) patients developed NT (toxicity group), leaving 17 (30%) without NT (nontoxicity group). Of the 39 patients, 14 (25%) were in the risk group, nine (16%) were in the injury group, and 16 (29%) were in the failure group. Twelve patients required renal replacement therapy. Sadly, 14 patients with NT died before colistin therapy ended. Among the survivors with NT (n = 25), NT did not resolve in five patients.

3.3. Main results

NT was seen after a median (IQR) of 5.0 (3.0–7.0) days (min–max: 2–16). ICU mortality was slightly higher in the NT group (P = 0.047). The length of ICU stay was also higher. There was no significant difference between the groups with and without NT for SAPS II scores, sex,

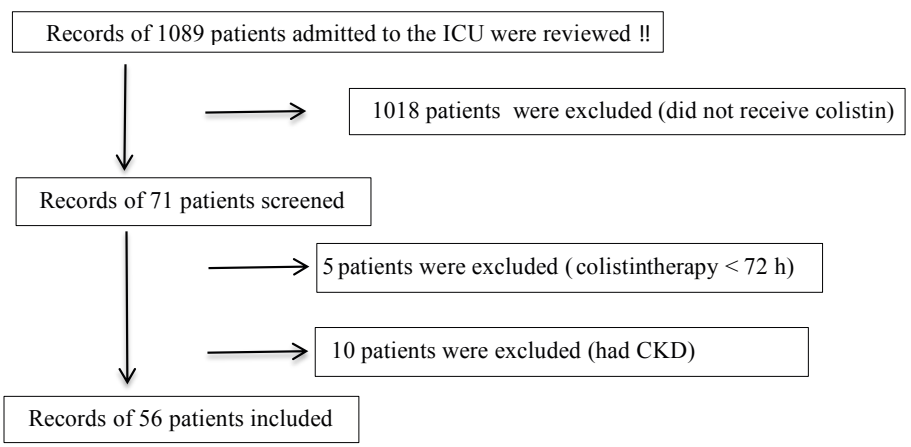

Figure. Flow diagram of study screening.

admission diagnosis, baseline creatinine levels, coexistence of sepsis, and exposure to nephrotoxic factors. The mean age and frequency of VP use was significantly higher in the toxicity group, while albumin levels were significantly lower (Table 2). ROC curves were generated to determine the clinically relevant cut-off for age and albumin levels as a predictor of NT. Analysis of the ROC curves showed that the discriminative ability was reasonable for albumin (AUC = 0.70, 95% CI = 0.541–0.856) with a cut-off value of 2.65 mg/dL and poor for age (AUC = 0.64, 95% CI = 0.468–0.819) with a cut off value of 46 years. NT rates were 79.5% in older patients compared with 33.3% in younger patients. Similarly, patients with lower albumin levels had higher NT rates (81.1%) than patients with higher levels (52.6%).

The use of VPs had a PPV and NPV for NT of 90% and 41.7% (RR = 1.543), respectively, while low albumin levels had values of 81.1% and 52.6% (RR = 1.712) and older age 79.5% and 66.7% (RR = 2.386), respectively.

No variables, with the exception of VP use, showed a statistically significant difference among patients who survived and those who did not (Table 3).

The risk of mortality in the NT group who received VPs was 1.65 times that of patients that did not receive VPs. Receiving VPs had a PPV of 94% for mortality. The correlation coefficient (phi), PPV, NPV, RR, and ORs of the predictors are listed in Table 4.

4. Discussion

The rate of nephrotoxicity in intensive care patients who used colistin, which is the primary objective of our study, was determined as 70%. This rate was higher than in previous studies. This may be due to the fact that our study was performed in a 3rd stage intensive care unit, the height of the saps2 scores, and the excess of accompanying diseases of the patients. Various criteria have been used to identify NT. The sensitivity of the RIFLE criteria in detecting AKI is high and it may have also contributed to the high incidence of NT.

The RIFLE criteria have been suggested for comparison of NT among different studies (21,22). Hartzell et al. demonstrated a NT rate of 45% in their cohort using the RIFLE criteria. However, their study group consisted of relatively young patients with lower comorbidities (21).

Temocin et al. reported a similarly low NT rate (48%); however, they did not specify the disease severity scores or comorbidities of patients, which may contribute to NT (23).

Similar to our results, Omrani et al. reported higher rates (71%) of NT; however, their study population was younger and not all were ICU patients (24).

Table 2. Characteristics of patients with and without nephrotoxicity.

	Whole cohort (56)	No NT (17)	NT (39)	P
Age[a]	64.09 ± 20.89	53.35 ± 25.27	68.77 ± 17.00	0.031
Male [b]	29	8	21	0.640
SAPS [c]	47.50 (42.25–60.00)	46.00 (43.50–50.00)	48.00 (41.00–64.00)	0.276
Medical Surgery Trauma	38 11 7	12 1 4	26 10 3	0.093
Albumin [a]	2.28 ± 0.49	2.51 ± 0.55	2.18 ± 0,44	0.019
Cr level[c]	0.95 (0.7–1.2)	0.80 (0.55–1.10)	1.00 (0.70–1.30)	0.183
VAP / BSI UTI / SSI	30 / 13 1 / 8	6 / 4 1 / 4	24 / 9 0 / 4	0.199
Sepsis	18	6	12	0.739
NT agents[b]	9	3	6	0.832
VPs [b]	20	2	18	0.016
ICU day[c]	37.50 (21.50–73.00)	28.00 (18.50–48.50)	43.00 (29.00–90.00)	0.038
Mortality[b]	37	8	29	0.047

a: Independent t test, mean (SD);
b: Pearson chi square test (exact);
c: Mann–Whitney U test, median (IQR)

Table 3. Characteristics of nephrotoxicity group with and without mortality.

	No mortality (10)	Mortality (29)	P
Age [a]	63.50 (36.50–73.00)	73.00 (61.00–78.00)	0.074
Male sex [b]	6	15	0.726
SAPS II [c]	52.00 ± 10.61	51.93 ± 16.25	0.990
Medical Surgery Trauma	6 2 2	20 8 1	0.280
Albumin level [c]	2.30 ± 0.53	2.14 ± 0.40	0.323
Baseline Cr [a]	0.85 (0.50–1.15)	1.10 (0.75–1.35)	0.175
Sepsis [b]	2	10	0.462
VPs [b]	1	17	0.008
Nephrotoxic agents[b]	2	4	0.639
NT day[a]	6.0 (3.5–13.25)	5.0 (3.0–7.0)	0.256

a: Mann–Whitney U test, median, (IQR)
b: Pearson chi square test (exact)
c: Independent t test, mean ± SD

Table 4. Correlation coefficient (phi), predictive values, relative risks, and odds ratios of predictors for nephrotoxicity and mortality in the nephrotoxicity group.

		PPV	NPV	RR	OR	Phi	P
NT	Alb	0.81	0.53	1.71 (1.04–2.82)	4.76 (1.41–16.13)	0.347	0.014
	VPs	0.90	0.42	1.54 (1.13–2.11)	6.43 (1.29–2.11)	0.330	0.016
	Age	0.79	0.67	2.39 (1.06–5.39)	7.78 (1.91–31.73)	0.412	0.004
Mortality	VPs	0.94	0.42	1.65 (1.12–2.23)	12.75 (1.42–114.4)	0.426	0.008

NPV: Negative predictive value
PPV: Positive predictive value
RR: Relative risks
OR: Odds ratios
Alb: Albumin

Some recent studies have investigated the risk factors for colistin-associated NT (8,21,24–34). Results from previous studies are given with their significance levels in Table 5. These studies show different results for each risk factor.

Factors that facilitate the development of nephrotoxicity in intensive care patients using colistin, a secondary objective of our study, were older age, lower albumin levels, and the use of vasopressors. These factors were compatible with previous studies. On the other hand, we also found that sepsis and septic shock, which had different outcomes in the literature, had no effect on nephrotoxicity.

Age was the most significant predictor in our study. It has the highest RR and NPV among all predictors for NT. Balkan et al. reported NT rates similar to ours in similar age groups (28). Other studies with large numbers of patients also found age to be an important risk factor (26,30). However, in a relatively young cohort of patients, no significant correlation between age and NT was shown. This may be explained by the effect of age on renal functional reserve.

Different albumin levels have been investigated in various studies to determine hypoalbuminemia. Kim et al. found that albumin levels lower than 3.2 g/dL were

Table 5. Reference numbers of studies evaluating colistin associated NT.

		P < 0.05	P > 0.05
Age		24, 25, 26, 28, 30	8, 21, 27, 29, 31, 32
Sex		-	8, 21, 24, 25, 26, 27, 28, 29, 31, 33
Body weight		25	24, 26, 27, 28
Disease severity		29 (SAPS II)	21, 25, 26, 27, 28, 30 (APACHE II)
Comorbidity	CCI DM HT	26, 28 25, 31 27	8, 24, 31, 33 8, 24, 27, 28 8, 28
Dose		-	8, 21, 24, 25, 28, 30, 32, 34
Duration		21, 26	8, 24, 27, 28, 29, 34
Creatinine		-	21, 27, 28
Severe sepsis		26, 29	26, 31, 34
Albumin		8, 24, 26	25, 28
VPs		-	21, 27, 31
Aminoglycoside		33	21, 24, 26, 27, 28, 33, 34
NSAID		26	21, 24, 27, 28, 33
Contrast media		27, 34	28, 21, 24, 33
Diuretics		26, 31	21, 24, 27, 33, 34

CCI: Carlson comorbidity index

associated with higher NT rates. However, in another study, which defined hypoalbuminemia as levels lower than 2.0 g/dL, no significant difference was observed. Studies comparing the mean albumin levels had different results. We observed a significant correlation between albumin levels and NT rates; ROC curve analysis showed an optimal cut-off value of 2.65 g/dL. The use of VPs was the third and last predictor of NT in our study. It had the highest PPV among the three predictors. In the literature, there are not sufficient data to use VP as a risk factor for colistin-associated NT. In a small cohort 40% of patients who had developed NT had received VPs, whereas in the nontoxicity group none of the patients had used VPs (20). However, other studies did not report any significant relationship between NT and the use of VPs (21,27,31).

Although sepsis is evaluated as one of the most common contributing factors in AKI of critical illness, the data are insufficient to conclude that colistin-associated NT is related to sepsis or septic shock.

Two large studies demonstrated that patients with septic shock had a higher incidence of NT (26–29).

However, a prospective study did not identify septic shock as a risk factor for sepsis (34). Similarly, Pogue et al. reported no significant correlation between sepsis and NT rates (31).

In the present study, we did not assess severe sepsis and septic shock separately, and we found no difference between the groups who did or did not have severe sepsis/septic shock. The association between NT and mortality has been discussed in earlier studies. Falagas et al. reported in their large cohort that creatinine change during colistin therapy was associated with mortality (aOR = 0.21) (11). In a recent study, no correlation was observed between mortality and NT; however, the number of patients in the NT group was small (n = 6) (35).

We could not find any published data assessing the risk factors for mortality among patients with colistin-associated nephropathy. The only risk factor for mortality we identified was the use of VPs, which had a PPV as high as 94%.

5. Limitations

One of the limitations of our study was the relatively small number of patients for logistic regression analysis. As such, we were unable to conclude whether or not the risk factors for NT would be statistically significant in the model. In

addition, we did not assess severe sepsis and septic shock separately. Although there was no statistically significant relationship between sepsis and NT, patients who received VPs had significantly higher NT rates. Because we had no data on the reason for VP use, we were unable to determine if it was associated with septic shock or other shock states. Therefore, we cannot draw any conclusions regarding the correlation between septic shock, VP use, and NT.

In conclusion, older age, hypoalbuminemia, and the use of VPs can contribute to colistin-associated NT in ICU patients. The use of VPs was identified as the only factor associated with mortality in patients who developed NT.

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