Factors Determining Nephrotoxicity and Mortality in Critical Care Patients Receiving Colistin

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Abstract
Introduction: We aimed to determine risk factors for nephrotoxicity and factors affecting mortality in patients who received colistin.
Methodology: Critical patients who received colistin were enrolled. Pregnancy, age < 18 years, basal creatinine level > 2 mg/dL, colistin use for < 48 hours, and previous renal replacement therapy were exclusion criteria. KDIGO stages were determined according to creatinine levels. Patients were grouped as those with no acute kidney injury (Group N0) and those with acute kidney injury (Group N). Their demographic data, APACHE II and SOFA scores, treatments, and laboratory results were recorded.
Results: A total of 91 patients were included: 27 in Group N0 and 64 in Group N. Demographic data were similar between groups; however, higher admission APACHE-II scores (OR:1.179, 95% CI:1.033-1.346, p = 0.015) and need for vasopressors (OR:5.486, 95% CI:1.522-19.769, p = 0.009) were found to be independent risk factors for nephrotoxicity. Higher APACHE II scores (OR:1.253, %95 CI:1.093-1.437, p = 0.001), presence of coronary artery disease (OR:7.720, %95 CI:1.613-36.956, p = 0.011), need for vasopressors (OR:4.587, %95 CI:1.224 – 17.241, p = 0.024), hypoalbuminemia (OR: 4.721, % 95 CI: 1.088 – 20.469, p = 0.038), and higher direct bilirubin levels (OR: 1.806, %95 CI: 1.055 – 3.092, p = 0.031) were independent risk factors for mortality.
Conclusion: When use of colistin is considered in ICU patients, presence of modifiable risk factors for nephrotoxicity such as hypoalbuminemia, nephrotoxic drug administration, and presence of shock should be determined and managed to prevent nephrotoxicity.

Key words: colistin; renal failure; risk factors; prognosis; mortality.

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Introduction
Multi-drug resistant (MDR) Gram-negative bacteria, particularly Acinetobacter and Pseudomonas species, are a major cause of life-threatening infections in intensive care units (ICU), and intense use of antibiotics overall is contributing to their increased resistance. For the treatment of these infections, higher dosages of antibiotics, longer infusion times, and the use of the previously used nephrotoxic and neurotoxic drug, colistin have been the current practices [1]. Colistin-related nephrotoxicity rate has been reported to range between 0-53.5% from different clinical studies. Both of these adverse effects of colistin are considered to be dose dependent, usually mild and reversible [2,3]. Such a wide range of rates may suggest the presence of modifiable reasons affecting the risk of nephrotoxicity.

The presence of acute kidney injury (AKI) is known to be associated with increased mortality in critically ill patients [4]. Therefore, it is conceivable that morbidity and mortality may be decreased by determination and correction of modifiable risk factors for AKI in patients receiving colistin treatment for infections with (MDR) Gram-negative bacteria. Injury caused by colistin is thought to be associated with oxidative damage and acute tubular necrosis [3,5]. Experiments on animals have shown that colistin nephrotoxicity may be prevented with treatment options having anti-oxidant effects [6,7].

In this study, we aimed to investigate the potential risk factors that may be associated with colistin nephrotoxicity and to determine factors that may affect the mortality of patients on colistin therapy to ensure safer use of colistin during infections with MDR Gram-negative bacteria.

Methodology
This retrospective study was conducted in the 20-bed, third-level Critical Care Unit of the Department of Anesthesiology and Reanimation at the Ankara Ataturk Training and Research Hospital between 2010 and 2012. Hospital records of patients with infections caused by MDR Gram-negative bacteria and who were administered colistin were reviewed after approval by the Yıldırım Beyazit
University, Hospital Ethics Committee (numbered B.30.2.YBU.006.06.01/32).

Patients younger than 18 years old, pregnant women, those whose basal creatinine value was greater than 2 mg/dL on admission, those who received colistin for less than 48 hours, and those who needed renal replacement treatment (RRT) prior to colistin initiation were excluded from the study. For patients with multiple episodes of colistin treatment, only the first was included in the analysis. Demographic characteristics, comorbidities, the type of ICU admission (medical/surgical, trauma), and Acute Psychology and Chronic Health Evaluation II (APACHE II) [8] and Sequential Organ Failure Assessment (SOFA) scores [9] from where the patient was transferred were noted. Hospital admission creatinine level, ongoing need for RRT at discharge from the ICU, indication for colistin treatment, date of colistin initiation, hospital and ICU outcomes, and treatment details including other drugs administered were also recorded.

During the study period, recommended colistin doses were 3-6 MIU of colistin per day, without a loading dose. (1 MIU is equivalent to approximately 30 mg colistin base activity). Colistin vials present in the hospital (Colimycin, Koçak Pharma, Istanbul, Turkey) contained 150 mg base colistin each, in the form of colistimethate sodium. Daily dose was administered as 75 mg IV tid or 150 mg IV bid; for patients with reduced creatinine clearance, the dosages were adjusted [10]. Colistin inhalation therapy was administered as nebulized therapy 75 mg twice a day. Inhalation therapy was included in the treatment regimen upon recommendation by an infectious diseases specialist; depending on the clinical progress of patients with pneumonia under intravenous colistin treatment.

Kidney Disease/Improving Global Outcomes (KDIGO) classification recommended for diagnosis and classification of AKI was adapted for the study [11]. AKI was accepted to be present when an increase in serum creatinine of > 0.3 mg/dL within 48 hours or when a minimum 1.5 times increase from basal value was observed. AKI stages were defined in accordance with the KDIGO classification of AKI: Stage 1: 1.5 to 1.9 times baseline creatinine or > 0.3 mg/dL increase from baseline, stage 2: 2 to 2.9 times increase from baseline, stage 3: 3 times increase from baseline, increase in serum creatinine to ≥ 4 mg/dL or initiation of renal replacement therapy. The patients were grouped as patients without acute kidney injury (Group N0) and those with acute kidney injury (Group N).

Statistical analysis

The distributions of continuous variables such as age, albumin was examined by Shapiro-Wilk’s test. These were expressed as median (min-max), because of the violation of the normality. Frequency and percentage were used for categorical variables.

Mann-Whitney U test and Chi-square tests were performed to compare patients with acute kidney injury to those without acute kidney injury and the alive patients to dead ones, according to continuous and categorical variables, respectively. The possible factors affecting the acute kidney injury and the mortality were determined by univariate binary logistic regression analysis. The multivariate binary logistic regression models were constructed for both two binary outcomes with the factors having significance value less than and equal to 0.250 in the univariate analysis, via Forward Likelihood ratio variable selection method. The possible factors which affect the KDIGO stages were obtained by univariate ordinal logistic regression analysis. The multivariate ordinal logistic regression model was constructed with the factors having significance value less than and equal to 0.250 in the univariate analysis, via backward variable selection method. Some insignificant variables were kept in the multivariate models, since their contributions to the model were found significant. The significance level was set as p < 0.05.

All statistical computations and analysis were performed by using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

Results

A total of 145 patients were administered colistin because of infections caused by MDR Gram-negative bacteria during the study period. Only 91 were included in the study, after screening for the exclusion criteria. Of these patients, 5 also received colistin inhalation therapy. AKI was observed in 64 (70.3%) of patients. When demographic and other hospitalization related characteristics were examined, patients with and without AKI were found to be similar except for the APACHE II score (Table 1). Median APACHE II scores for patients with AKI (Group N) and without AKI (Group N0) were 18 (min-max:12-30) and 20 (min-max:12-37), respectively (p = 0.024). Hospitalization SOFA scores were similar. Microbiological cultures from patients, revealed Acinetobacter baumannii in 75.8% of the cases. Indications for initiation of colistin therapy were similar between the groups (Table 2).

Even though there was no difference between the initial creatinine levels, creatinine levels on day 14 were higher in patients with AKI (Table 3). Median creatinine level on day 14 was 1.49 mg/dL in Group N and 0.63 mg/dL in Group N0 (p=0.003). ICU mortality for group N and group N0 were 64.1% (n = 41) and 37.0 % (n = 10), respectively (p = 0.032) (Table 4).

The results of univariate analysis for risk factors of acute renal injury showed that there were statistically significant differences in APACHE II score and need for vasopressor treatment on any day of colistin therapy between the two groups (p<0.05). Multivariate logistic regression analysis showed that APACHE II score (OR = 1.179, 95% CI = 1.033-1.346, p = 0.015) and need for vasopressor treatment on any day of colistin therapy (OR = 5.486, 95% CI = 1.522 – 19.769, p = 0.009) were independent risk factors for acute renal injury (Table 5).
When factors that might affect KDIGO stages during colistin nephrotoxicity were evaluated, ICU admission for surgical reasons and need for vasopressor treatment on any day of colistin therapy were associated with higher KDIGO stages. On the other hand, higher albumin levels were associated with lower KDIGO stages (p < 0.05). Upon multivariate analysis, need for vasopressor treatment on any day of colistin therapy (OR = 3.146, 95% CI: 1.435–6.903, p = 0.019) and concomitant administration of NSAIDs (OR = 2.540, 95% CI: 1.157–5.797, p = 0.005) remained independent factors for higher KDIGO stage (Table 6).

When factors associated with mortality were evaluated, patients who were lost were found to be older (p = 0.028). Creatinine levels on initiation of colistin, last recorded creatinine level, total bilirubin, direct bilirubin, maximum total bilirubin and maximum direct bilirubin levels were found to be higher in those who were lost in the ICU. On the other hand, initial albumin levels were higher in survivors (p = 0.005). AKI rate was lower in survivors (57.5%, p = 0.032) (Table 7).

Univariate analysis revealed that age, admission APACHE II and SOFA scores, presence of coronary artery disease (CAD) or severe heart failure, ICU discharge creatinine levels, APACHE II and SOFA scores at initiation of colistin, presence of hypovolemic shock while starting colistin were determined as factors increasing risk of mortality (p < 0.05). Initial colistin dosage, mean colistin dose, initial and mean albumin levels were found to be factors associated with improved survival (p=0.05). Result of multivariate analyses revealed that presence of CAD (OR = 7.720, 95% CI: 1.613 – 36.956, p = 0.011), the need for vasopressor treatment on any day of colistin therapy (OR = 4.587, 95% CI: 1.224 – 17.241, p = 0.024), APACHE II score at colistin initiation (OR = 1.253, 95% CI: 1.093 – 1.437, p = 0.001), and maximum direct bilirubin level (OR = 1.806, 95% CI: 1.055 – 3.092, p = 0.031) were associated with increased mortality independent of other factors; mean albumin level was inversely associated with mortality (OR = -4.721, 95% CI: 1.088 – 20.469, p = 0.038) (Table 8).

Discussion
This study aimed to determine the risk factors associated with nephrotoxicity during treatment of MDR Gram-negative bacterial infections with colistin. A great majority of patients who received colistin were admitted for medical reasons. However, colistin related nephrotoxicity, was observed more commonly in patients who were admitted for surgery or trauma. Most frequent reason for colistin initiation was isolation of MDR A. baumannii from endotracheal aspirate and blood cultures. The main finding of our study was that high admission APACHE II scores and the need for vasopressor treatment during colistin treatment was associated with increased risk of developing nephrotoxicity. Mortality was higher in patients with nephrotoxicity. The presence of coronary artery disease, higher APACHE II scores on colistin initiation, need for vasopressors during colistin treatment, higher bilirubin and lower albumin levels were the independent factors associated with mortality in patients on colistin therapy.

Studies on AKI use AKIN, RIFLE or KDIGO criteria for classification. However, Spapen et al [2] have reported that nephrotoxicity frequency and severity may differ depending on the classification criteria used. In the study by Akajagbor et al [12], in which they studied the side effects of colistin in 173 patients, the frequency of nephrotoxicity has been reported to be 60.4% using RIFLE criteria. Hartzell et al [13] have also used RIFLE criteria and reported colistin related nephrotoxicity rate as 45% in their studies. In our study, we used KDIGO classification, and colistin related nephrotoxicity rate was found to be 70.3%. If RIFLE criteria had been adopted, this rate would have been 57.4%. This is because 0.3 mg/dL increase in serum creatinine or 1.5-2 times increase in basal creatinine is considered as stage I AKI according to KDIGO staging, whereas 1.5 times increase in serum creatinine level points to risk stage in RIFLE classification. Patients who do not meet RIFLE Risk stage criteria are included in KDIGO AKI stage 1. Thus, KDIGO classification is more sensitive to detect AKI [14]. Consequently, this increases the nephrotoxicity rate when KDIGO classification is preferred. In our study, the use of KDIGO classification could have resulted in higher nephrotoxicity rates than the literature.

Table 1. Baseline Characteristics of the Study Patients.

| Characteristic                  | Group N (n = 64) | Group N₀ (n = 27) | p value |
|--------------------------------|-----------------|------------------|--------|
| Age, y, median (min-max)       | 70.0 (26 – 90)  | 65.0 (26 – 86)   | 0.234 |
| Female:male [n(%)]             | 29.35 (45.3%:54.7%) | 16:11(59.3%:40.7%) | 0.324 |
| BMI*, median (min-max)         | 26.83 (17.75 – 60.55) | 26.77 (19.03 – 36.33) | 0.897 |
| Admission APACHE II median     | 20 (12-37)      | 18 (12-30)       | 0.024 |
| Admission SOFA median          | 7 (1-13)        | 6 (1-15)         | 0.200 |
| Type of ICU admission          |                 |                  | 0.103 |
| Surgical/trauma                | 22 (34.4 %)     | 4 (14.8 %)       | 0.843 |
| Medical                        | 42 (65.6 %)     | 23 (85.2 %)      | 0.103 |
| Transferring ward              |                 |                  | 0.843 |
| Hospital ward                  | 48 (75.0 %)     | 19 (70.4 %)      | 0.843 |
| Emergency services             | 16 (25.0 %)     | 8 (29.6 %)       | 0.843 |

Data are reported as n (%), unless specified; BMI: body mass index, *n = 53 for Group N and n = 23 for Group N₀.
Table 2. Indications for Colistin Therapy Initiation.

| Indication for colistin initiation                      | Group N (n = 64) | Group N₀ (n = 27) | p value |
|---------------------------------------------------------|------------------|------------------|---------|
| Isolation of A. baumanii from ETA cultures             | 31 (48.4 %)      | 10 (37.0 %)      |         |
| Isolation of A. baumanii from blood cultures           | 9 (14.1 %)       | 8 (29.6 %)       |         |
| Gram (-) signal from ETA cultures                      | 2 (3.1 %)        | 2 (3.1 %)        | 0.329   |
| Gram (-) signal from blood cultures                    | 13 (20.3 %)      | 4 (14.8 %)       |         |
| Isolation of A. baumanii from urine or wound cultures  | 3 (4.7 %)        | 0                |         |
| Decision of physician based on clinical findings       | 6 (9.4 %)        | 4 (14.8 %)       |         |

Data are reported as n (%), ETA: endotracheal aspirate.

Table 3. Comparison of Laboratory Values of the Cases in Groups.

| Parameter                               | Group N (n = 64) | Group N₀ (n = 27) | p value |
|-----------------------------------------|------------------|------------------|---------|
| Creatinine on day 0                     | 0.70 (0.20 – 2.00) | 0.70 (0.09 – 1.98) | 0.571   |
| Creatinine on day 14*                   | 1.49 (0.30 – 5.60) | 0.63 (0.10 – 1.29) | **0.003** |
| Maximum creatinine                      | 1.84 (0.30 – 6.20) | 0.90 (0.30 – 2.02) | < **0.001** |
| Albumin on day 0                        | 2.78 (1.20 – 3.70) | 2.90 (2.40 – 3.40) | 0.104   |
| Total bilirubin on day 0                | 0.70 (0.18 – 10.00) | 0.60 (0.20 – 3.00) | 0.257   |
| Maximum total bilirubin                 | 1.10 (0.00 – 19.00) | 0.90 (0.30 – 8.30) | 0.239   |
| Direct bilirubin on day 0               | 0.35 (0.07 – 9.90) | 0.30 (0.10 – 2.10) | 0.182   |
| Maximum direct bilirubin               | 0.60 (0.17 – 16.00) | 0.50 (0.10 – 6.20) | 0.131   |

Data are reported as median (min-max); * n = 27 for Group N and n = 14 for Group N₀.

Table 4. Outcome Variables of Groups.

| Outcome                                | Group N (n = 64) | Group N₀ (n = 27) | p value |
|----------------------------------------|------------------|------------------|---------|
| ICU LOS*, median (min-max)             | 47.0 (1 – 260)   | 44.0 (8 – 184)   | 0.610   |
| ICU mortality, n (%)                   | 41 (64.1)        | 10 (37.0)        | **0.032** |

LOS: length of stay, * n = 63 for Group N.

Table 5. Multivariate Logistic Regression Analysis of Variables Related to Acute Kidney Injury.

| Parameter                          | OR    | 95 CI            | p value |
|------------------------------------|-------|-----------------|---------|
| Admission APACHE II                | 1.179 | 1.033 – 1.346    | **0.015** |
| Need for vasopressors*             | 5.486 | 1.522 – 19.769   | **0.009** |
| N-acetylcysteine dosage            | 1.005 | 0.999 – 1.010    | 0.079   |

* need for vasopressor treatment on any day of colistin therapy.

Table 6. Multivariate Logistic Regression Analysis of the Possible Factors Affecting KDIGO Stage.

| Parameter                          | OR    | 95 CI            | p value |
|------------------------------------|-------|-----------------|---------|
| Need for vasopressors* (Yes/No)    | 3.146 | 1.435-6.903     | **0.019** |
| Simultaneous NSAID intake (Yes/No) | 2.540 | 1.157-5.579     | **0.005** |

* need for vasopressor treatment on any day of colistin therapy; NSAID: Nonsteroidal anti-inflammatory drug.
Table 7. Characteristics of Patients When Grouped According to Their ICU Outcome.

| Characteristic                                    | Survivors (n = 40) | Exitus (n = 51) | p value |
|--------------------------------------------------|--------------------|-----------------|---------|
| Age, y, median (min-max)                         | 64.5 (26 – 88)     | 72.0 (26 – 90)  | 0.028   |
| Sex ratio                                        |                    |                 |         |
| Female:male [n(%)]                               | 22:18 (55.0%;45 %) | 23:28 (45.1%;54.9%) | 0.468   |
| BMI*, median (min-max)                           | 27.76 (19.03 – 42.02) | 26.57 (17.75 – 60.55) | 0.091   |
| Admission APACHE II median (min-max)             | 18(12-30)          | 21(12-37)       | 0.005   |
| Admission SOFA median (min-max)                  | 6(1-11)            | 7(1-15)         | 0.009   |
| **Type of ICU admission**                        |                    |                 |         |
| Surgical/trauma                                  | 10 (25.0 %)        | 35 (68.6 %)     | 0.326   |
| Medical                                          | 30 (75.0 %)        | 16 (31.4 %)     |         |
| **Transferring ward**                            |                    |                 |         |
| Hospital ward                                    | 32 (80.0 %)        | 35 (68.6 %)     |         |
| Emergency services                               | 8 (20.0 %)         | 16 (31.4 %)     |         |
| **Indication for colistin initiation**           |                    |                 |         |
| Isolation of *A. baumanii* from ETA cultures     | 18 (45.0%)         | 23 (45.1%)      |         |
| Isolation of *A. baumanii* from blood cultures   | 11 (27.5%)         | 6 (11.8%)       |         |
| Gram (-) signal from ETA cultures                | 2 (5.0%)           | 1 (2.0%)        | 0.124   |
| Gram (-) signal from blood cultures              | 5 (12.5%)          | 12 (23.5%)      |         |
| Isolation of *A. baumanii* from urine or wound cultures | 0 (0.0%)          | 3 (5.9%)        |         |
| Decision of physician based on clinical findings | 4 (10.0%)          | 6 (11.8%)       |         |
| Creatinine on day 0, median (min-max)            | 0.60 (0.09 – 1.98) | 0.70 (0.20 – 2.00) | 0.040   |
| Creatinine on day 14, median (min-max)**         | 0.80 (0.10 – 2.20) | 1.10 (0.40 – 5.60) | 0.277   |
| Last creatinine level, median (min-max)          | 0.85 (0.10 – 2.90) | 1.40 (0.24 – 5.60) | 0.049   |
| Albumin on day 0, median (min-max)               | 2.90 (2.30 – 3.70) | 2.70 (1.20 – 3.30) | 0.005   |
| Total bilirubin on day 0, median (min-max)       | 0.52 (0.20 – 2.90) | 0.80 (0.18 – 10.00) | 0.005   |
| Direct bilirubin on day 0, median (min-max)      | 0.30 (0.08 – 2.10) | 0.50 (0.07 – 9.90) | 0.005   |
| Maximum total bilirubin, median (min-max)        | 0.85 (0.00 – 4.80) | 1.50 (0.40 – 19.00) | 0.004   |
| Maximum direct bilirubin, median (min-max)       | 0.42 (0.10 – 3.90) | 0.90 (0.18 – 16.00) | 0.001   |
| ICU LOS, median (min-max)***                     | 58.5 (1 – 225)     | 36.0 (2 – 260)  | 0.088   |
| **Presence of AKI**                              |                    |                 |         |
| No                                               | 17 (42.5 %)        | 10 (19.6%)      | 0.032   |
| Yes                                              | 23 (57.5%)         | 41 (80.4%)      |         |

* n = 37 for alive and n = 39 for exitus; ** n = 24 for alive and n = 17 for exitus; *** n = 50 for exitus; Data are reported as n (%) unless specified; BMI: body mass index, ETA: endotracheal aspirate, ICU LOS: intensive care unit length of stay, AKI: acute kidney injury.

Table 8. Multivariate Logistic Regression Analysis of Variables Affecting Mortality.

| Parameter                                | OR     | % 95 CI         | p value |
|------------------------------------------|--------|-----------------|---------|
| CAD*                                     | 7.720  | 1.613 – 36.956  | 0.011   |
| Severe heart failure                     | 3.751  | 0.977 – 14.395  | 0.054   |
| Mean colistin dose                       | 0.996  | 0.986 – 1.007   | 0.473   |
| Mean albumin (inverse effect)            | 4.721  | 1.088 – 20.469  | 0.038   |
| Maximum direct bilirubin                | 1.806  | 1.055 – 3.092   | 0.031   |
| Need for vasopressors**                  | 4.587  | 1.224 – 17.241  | 0.024   |
| APACHE II (at colistin initiation)       | 1.253  | 1.093 – 1.437   | 0.001   |
| Acute kidney injury                      | 2.117  | 0.619 – 7.241   | 0.232   |

*Coronary artery disease, **need for vasopressor treatment on any day of colistin therapy.
In elderly, there is a regression in the kidney functions, and creatinine levels may not correctly reflect the kidney functions. DeRyke et al [15] found nephrotoxicity incidence significantly higher in the elderly population, in a 30-patient retrospective study on patients receiving colistin. In our study, average age of patients with AKI was higher, but the difference was not statistically significant. Although age was found to be related with increased mortality in univariate analysis, this relation was lost in the multivariate analyses.

In a meta-analysis of 26 studies on nephrotoxicity with colistin, it was reported that nephrotoxicity could develop even following 48 hours of colistin treatment. It was reported that old age, hypoalbuminemia, underlying chronic kidney disease and septic shock could further increase the risk of nephrotoxicity, but the nephrotoxicity was reversible. In our study, among these factors, only the presence of shock was determined as a risk factor for nephrotoxicity and mortality. While hypoalbuminemia could not be shown as an independent variable related with nephrotoxicity, it was shown to be related to mortality [2]. Renal functions showed improvement in 20 (31.2%) of the patients in our study during their stay in the ICU. This rate would probably have been higher if the patients had been followed after their stay in ICU.

In a study by Rattanaumpawan et al [16], it was reported that simultaneous use of colistin and nephrotoxic drugs (diuretics, aminoglycosides, NSAIDs), advanced age (> 65 years), presence of hypoalbuminemia, use of contrast media, dehydration, diabetes mellitus, chronic kidney disease and paraproteinemia increased the rate of nephrotoxicity. In their above mentioned study, De Ryke et al [15] found that the use of colistin together with nephrotoxic agents (such as diuretics) increased the risk of nephrotoxicity. In our study, it was shown that the simultaneous use of colistin and NSAIDs was a risk factor for higher KDIGO stage.

Komanachai et al [17], observed nephrotoxicity in 30.8% of the patients on colistin in their study. They reported that 70% of the patients developing nephrotoxicity had underlying chronic kidney disease, risk factors such as simultaneous use of other nephrotoxic drugs and hypovolemia; however, none of the patients with nephrotoxicity required RRT. There were a total of 3 patients requiring RRT during colistin treatment in our study. In accordance with other study results, in our study RRT requirement rate was very low and colistin toxicity was reversible in survivors [2,3].

Overall mortality rate was 56% in our study. When mortality was compared between groups with and without nephrotoxicity, mortality was 37% in Group N0 and 64.1% in Group N. Nephrotoxicity seemed to be associated with increased mortality rate and treatment failure. However, nephrotoxicity was not shown as an independent factor for mortality. This led us to think that emergence of nephrotoxicity could be a predictor of the severity of the underlying disease process. Higher admission APACHE II scores, despite similar admission SOFA scores among patients with nephrotoxicity also may support that these patients had more serious underlying comorbidities. Unlike SOFA scoring system, APACHE II includes points for older age and presence of chronic diseases.

Hyperbilirubinemia is known to be associated with poor prognosis in critical patients [18]. When we evaluated factors affecting mortality other than nephrotoxicity, the presence of CAD, need for vasopressor treatment, high APACHE II score while colistin initiation, hypoalbuminemia and high direct bilirubinemia were determined as the independent factors increasing mortality.

These results should be interpreted considering several limitations of the study. Firstly, retrospective and observational nature of the study could be considered the main limitation of the study. Since, information obtained mainly depended on hospital records, there was difficulty in verifying some parameters such as fluid balance. As well, for the same reason, no protocol could be created about antibiotic choices and the accompanying drugs; treatment was given in line with the recommendations of the consultant infectious diseases physicians. Secondly, the study was based on data included from a single center. Even though it is a mixed ICU, a multi-center study including different patient populations would have presented more robust results. Thirdly, the number of patients is limited since the study was conducted in a single center.

Conclusion
Infections caused by MDR Gram-negative bacteria are a world-wide problem, especially in developing countries. Consequently, the use of colistin has recently gained popularity, since alternative antibiotic options are limited. However, nephrotoxicity is the most important complication limiting the use of colistin. When use of colistin is considered, regarding the fact that AKI development could adversely affect morbidity and mortality, modifiable risk factors for AKI such as hypoalbuminemia, simultaneous use of nephrotoxic drugs and intervenable reasons such as presence of shock should be determined and treated. Nevertheless, our study results reveal that colistin nephrotoxicity is not independently associated with increased mortality, thus fear of nephrotoxicity should not preclude colistin utilization until a better option is available.

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