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# Polymyxin B vs. colistin: the comparison of neurotoxic and nephrotoxic effects of the two polymyxins

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## Abstract

**Background** The study aimed to compare polymyxin B with colistimethate sodium (CMS) regarding neurotoxicity, nephrotoxicity and 30-day mortality in patients with MDR Gram-negatives.

**Methods** All adult patients who received polymyxin B or CMS for at least 24 h for the treatment of MDR microorganisms were evaluated retrospectively.

**Results** Among 413 initially screened patients, 147 patients who were conscious and able to express their symptoms were included in the neurotoxicity analysis. 13 of 77 patients with polymyxin B and 1 of 70 with CMS had neurotoxic adverse events, mainly paresthesias. All events were reversible after drug discontinuation. Among 290 patients included in nephrotoxicity analysis, the incidence of acute kidney injury (AKI) was 44.7% and 40.0% for polymyxin B and CMS, respectively ($p=0.425$). AKI occurred two days earlier with colistin than polymyxin B without statistical significance (median (IQR): 5 (3–11) vs. 7 (3–12), respectively, $p=0.701$). Polymyxin therapy was withdrawn in 41.1% of patients after AKI occurred and CMS was more frequently withdrawn than polymyxin B ($p=0.025$). AKI was reversible in 91.6% of patients with CMS and 79% with polymyxin B after the drug withdrawal. Older age, higher baseline serum creatinine and the use of at least two nephrotoxic drugs were independent factors associated with AKI (OR 1.05, $p<0.001$; OR 2.99, $p=0.022$ and OR 2.45, $p=0.006$, respectively). Septic shock, mechanical ventilation, presence of a central venous catheter and Charlson comorbidity index (OR 2.13, $p=0.004$; OR 3.37, $p<0.001$; OR 2.47, $p=0.004$ and OR 1.21, p $p<0.001$, respectively) were the independent predictors of mortality. The type of polymyxin was not related to mortality.

**Conclusions** Neurotoxicity is a relatively common adverse event that leads to drug withdrawal during polymyxins, particularly polymyxin B. Nephrotoxicity is very common during polymyxin therapy and the two polymyxins display similar nephrotoxic events with high reversibility rates after drug withdrawal. Close monitoring of AKI is crucial during polymyxin therapy, particularly, for elderly patients, patients who have high baseline creatinine, and using other nephrotoxic drugs.

**Keywords** Colistin, Mortality, Nephrotoxicity, Neurotoxicity, Polymyxin B

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## Introduction

Polymyxins are polypeptide antibiotics that were first recognized in the 1940s. Despite having broad activity against Gram-negative bacteria, their use was abandoned due to their toxicity for many years [1]. Polymyxins were re-considered in recent years with the unavoidable rise of carbapenem-resistant Gram-negative bacteria. Five different polymyxins were initially recovered but only polymyxin B and colistin are currently available for clinical use. Polymyxin B and colistin demonstrate different pharmacokinetic (PK) properties despite having similar structures and antibacterial activities. Colistin (polymyxin E) is administered as its inactive prodrug, colistimethate sodium (CMS) converted into colistin in vivo. Polymyxin B is administered as its active form, and therefore it achieves plasma concentrations more rapidly than colistin [2]. There is relatively more significant interindividual variability in the PKs of CMS/colistin compared to polymyxin B. Although colistin was widely used previously, polymyxin B has become more favorable for clinicians in recent years because of these PK advantages. However, it is still unclear in the literature whether the PK advantage of polymyxin B is translated into clinical practice.

The most significant adverse events that limit the use of polymyxins are neurotoxicity and nephrotoxicity. Studies in the 1960s and 1970s showed high rates of neurological side effects ranging from 7 to 27%. Fewer studies have reported neurotoxicity after the 2000s and the incidence is lower than in previous ones [3]. Nephrotoxicity is the other significant and common adverse event leading to dose modifications and drug withdrawal. It is associated with longer hospital stays, increased costs and higher mortality risk in hospitalized patients [4, 5].

In our country, CMS has been used for many years and polymyxin B is now available since 2018. Both polymyxins are heavily used in clinical practice due to the high rates of carbapenem-resistant Gram-negative bacteria. Therefore, it is essential to elucidate whether there is a difference between the two polymyxins regarding safety and mortality to use polymyxins more efficiently. In this study, we aimed to compare polymyxin B with CMS regarding neurotoxicity, nephrotoxicity and 30-day mortality in patients infected with multi-drug resistant (MDR) Gram-negative bacteria.

## Methods

### Patient groups and study design

This retrospective cohort study was conducted between January 2018 and March 2023, in Gazi University Hospital, a 1007-bed teaching hospital. The study was approved by Gazi University Ethics Committee with decision number 11, on June 6, 2023.

All adult patients (>18 years) receiving polymyxin therapy, either as polymyxin B (Polix, Kocak Farma, Istanbul, Türkiye) or CMS (Colimycin, Kocak Farma, Istanbul, Türkiye) for at least 24 h for any type of infection were included in the study. Data were retrieved from the electronic records of patients. Data collection included demographics, comorbidities, laboratory findings (serum creatinine, albumin and glomerular filtration rates at baseline and during polymyxin therapy), symptoms potentially related to neurotoxicity, ICU admission, duration of polymyxins, concomitant use nephrotoxic drugs (aminoglycosides, loop diuretics, vasopressors, vancomycin, amphotericin B, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, contrast agents), type of infection and causative microorganisms. Only the first episodes of patients treated with polymyxins were included in the study if they had more than one treatment episode. CMS and polymyxin B were administered with daily doses of 300 mg and 2.5 mg/kg divided into 2 doses following loading doses of 300 mg and 2.5 mg/kg, respectively. Dose adjustments were made according to the glomerular filtration rate for CMS for patients with AKI occurrence. No dose adjustments were made for polymyxin B.

### Outcome measurements and definitions

The primary outcome of this study was to compare the neurotoxicity and nephrotoxicity of polymyxin B with CMS. Secondary outcomes were to assess the independent risk factors for nephrotoxicity and 30-day mortality. Neurotoxicity was assessed in all patients who were conscious and could express their symptoms by consultant infectious diseases doctors. Neurotoxicity was defined as the presence of paresthesia, numbness, seizure, muscle weakness, ataxia and altered mental status after polymyxin therapy [6]. Nephrotoxicity was assessed and staged according to "KDIGO- Acute Kidney Injury (AKI)" criteria [7]. While staging AKI, the highest serum creatinine value during the polymyxin therapy, was considered. Patients with chronic kidney diseases including end-stage kidney disease, and patients with acute kidney failure at the beginning of the study were excluded from nephrotoxicity analysis. Chronic kidney disease (CKD) was defined as the decrease of glomerular filtration rate below 60 ml/min/1.73 m2 for >3 months [8]. Baseline renal function was defined as the serum creatinine on the day of polymyxin initiation. Patients were followed until discharge from/death in hospital.

### Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, N.Y., USA). The variables were investigated using visual (histograms, probability plots) and analytical methods

(Kolmogorov- Simirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. The categorical variables were expressed as a number and a percentage, continued values were presented as a mean and standard deviation (SD) or median values and an interquartile range (IQR) of 25–75%. The categorical variables were analyzed with a Chi-square test or Fisher exact test. The non-parametric variables were analyzed using the Mann–Whitney U, and the parametric ones with a Student t-test. In the univariate analysis, variables with a *p*-value of less than 0.20 and not correlated with each other were included in the logistic regression model using backward LR selection. The variables included in the multivariate model were age, baseline creatinine, baseline albumin, the use of at least two nephrotoxic drugs, diuretics, vasoactive agents, amphotericin B, hypertension, chronic heart diseases and Charlson comorbidity index for nephrotoxicity analysis and age, ICU admission, septic shock, mechanical ventilation, central venous catheter, baseline albumin and creatinine, type of polymyxin, Charlson comorbidity index, bloodstream infection, skin-soft tissue infection and urinary tract infection for mortality analysis. Values with a type-I error level of below 5% were considered statistically significant.

## Results

413 patients who received either polymyxin B or CMS for the treatment of infections caused by gram-negative bacteria were screened and included in the study (Fig. 1). Polymyxins were used in combination with beta-lactams in 342 patients, tigecycline in 167, fosfomycin in 72 and aminoglycosides in 7 patients.

Neurotoxicity was assessed in 147 of 413 patients who were conscious and could express their symptoms, so neurotoxic effects were observed. The crude incidence of neurotoxicity was 9.5% during polymyxin therapy. The incidence was 18.3% (13/77) and 1.4% (1/70) among patients who received polymyxin B and CMS, respectively. Numbness and paresthesia in the face, tongue and/or extremities were reported in 11 patients, seizure in one patient and ataxia in one patient among patients who received polymyxin B whereas altered mental status was reported in one patient who received colistin. 9 of 14 patients experienced symptoms within the first 72 h of the drug and the median duration was 2 (IQR: 1-6.25) days. Characteristics of patients with and without neurotoxicity are presented in Table 1. Patients with neurotoxicity were younger than patients without neurotoxicity. Charlson comorbidity index was lower in the neurotoxicity group without statistical difference. Polymyxins were stopped in all patients with neurotoxicity and symptoms resolved in all patients after withdrawal of the drugs.

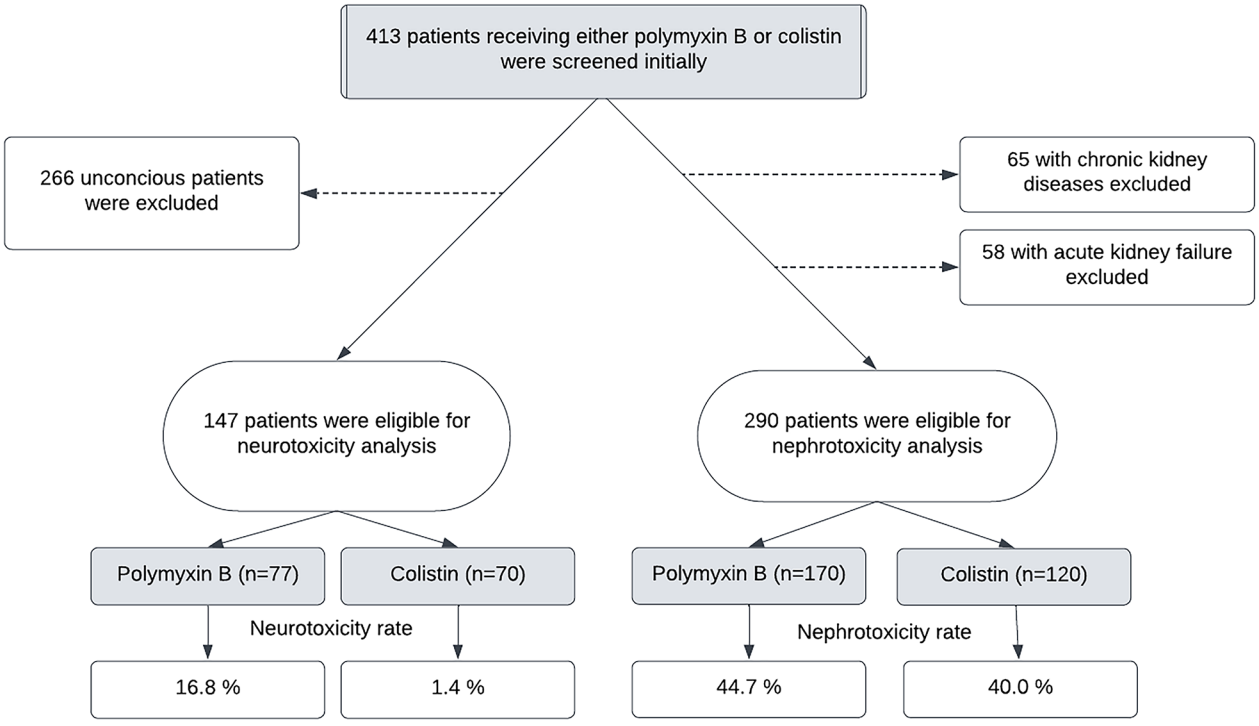


**Fig. 1** Flowchart of the study

**Table 1** Characteristics of patients with and without neurotoxicity

| | Patients with neurotoxicity (*n* = 14) | Patients without neurotoxicity (*n* = 127) | *p* |
|---|---|---|---|
| Age, median (IQR) | 50 (28-63.5) | 66 (53–74) | **0.005** |
| Gender, male | 7 (50.0) | 41 (32.3) | 0.195 |
| Baseline serum albumin, g/dL, median (IQR) | 2.9 (2.4–3.5) | 2.6 (2.3–2.9) | 0.091 |
| Baseline serum creatinine, mg/dL, median (IQR) | 0.5 (0.3–1.4) | 0.7 (0.5-1.0) | 0.181 |
| Type of polymyxin | | | |
| Polymyxin B | 13 (92.9) | 58 (45.7) | **0.001** |
| Colistin | 1 (7.1) | 69 (54.3) | |
| Nephrotoxicity during polymyxin therapy* (*n* = 127) | 1 (7.1) | 48 (42.5) | 0.010 |
| **Concurrent drugs** | | | |
| Diuretics | 3 (21.4) | 58 (45.7) | 0.082 |
| NSAIDs** | 1 (7.1) | 8 (6.3) | 1.000 |
| Vasoactive agents | 1 (7.1) | 22 (17.3) | 0.467 |
| Aminoglycosides | 0 (0) | 3 (2.4) | 1.000 |
| Voriconazole | 0 (0) | 2 (1.6) | 1.000 |
| Tacrolimus/sirolimus | 0 (0) | 1 (0.8) | 1.000 |
| **Comorbid diseases and conditions** | | | |
| Malignancy | 4 (28.6) | 56 (44.1) | 0.265 |
| Hypertension | 3 (21.4) | 54 (42.5) | 0.127 |
| Cardiovascular diseases | 4 (28.6) | 45 (35.4) | 0.609 |
| Chronic neurological disease | 2 (14.3) | 32 (25.2) | 0.365 |
| Diabetes mellitus | 4 (28.6) | 40 (31.5) | 1.000 |
| Chronic obstructive pulmonary disease | 2 (14.3) | 20 (15.7) | 1.000 |
| Chronic kidney disease | 2 (14.3) | 35 (27.6) | 0.356 |
| Charlson comorbidity score, median (IQR) | 2.5 (0–6) | 5 (3–7) | 0.069 |

* Patients with acute kidney failure and chronic kidney disease were excluded

** NSAID: Non-steroid anti-inflammatory drug

Symptoms also did not recur in four patients whose polymyxin B therapy was switched to CMS.

Among 413 screened patients, 65 with chronic kidney diseases and 58 with acute kidney failure were excluded, and a total of 290 patients (170 receiving polymyxin B and 120 cm) were then included in the nephrotoxicity analysis. The characteristics of patients are presented in Table 2.

The overall AKI rate for polymyxin B and CMS was similar (44.7% and 40.0%, $p=0.425$, Fig. 2). Although AKI occurred two days earlier with colistin than polymyxin B, this did not show statistical significance (median (IQR): 5 (3–11) vs. 7 (3–12) days, respectively, $p=0.701$). There is also no difference between polymyxin B and CMS in terms of the distribution of time until nephrotoxicity (Fig. 3). 24.2% of AKI cases were stage 1, 35.5% were stage 2 and 40.3% were stage 3. AKI stages were similar for polymyxin B and CMS (Fig. 4). Polymyxin therapy was withdrawn in 41.1% of patients after AKI occurred and CMS was more frequently withdrawn than polymyxin B ($p=0.025$) (Fig. 4). CMS was switched to polymyxin B in 14 patients after the occurrence of nephrotoxicity. The rate of reversal of nephrotoxicity for CMS and for polymyxin B was 91.6% and 79% for patients with drug withdrawal, 66.6% and 42.8% for patients with drug continuation, and 75% for patients whose CMS therapy switched to polymyxin B (Fig. 4).

Factors associated with nephrotoxicity were evaluated by univariate and multivariate analysis (Table 3). Multivariate analysis revealed that the independent risk factors for the onset of nephrotoxicity were older age, higher baseline creatinine and the use of at least two nephrotoxic agents.

Factors associated with mortality are shown in Table 4. All 413 patients were included in the analysis. Septic shock, mechanical ventilation, presence of a central venous catheter and Charlson comorbidity index were the independent predictors of mortality. Although mortality was higher in patients who received polymyxin B than CMS in the univariate analysis, multivariate analysis did not show any difference.

## Discussion

Our study presents detailed data on polymyxin-associated neurotoxicity which is scarce in the literature, and a comparison of nephrotoxicity between the two polymyxins. Our findings show that neurotoxicity is not rare during polymyxin therapy and it is mainly associated with polymyxin B. Facial and peripheral paresthesias were the most frequently observed manifestations. AKI during

**Table 2** Characteristics of patients included in the nephrotoxicity analysis

| | **Polymyxin B** ***n*** **= 170 (%)** | **CMS** ***n*** **= 120 (%)** | ***p*** |
|---|---|---|---|
| Age, median (IQR) | 66 (55–75) | 64.5 (52.2–71.7) | 0.178 |
| Gender, male | 105 (61.8) | 79 (65.8) | 0.479 |
| Intensive care unit admission | 131 (77.1) | 80 (66.7) | **0.050** |
| Septic shock | 50 (29.4) | 30 (25.0) | 0.408 |
| Duration of hospitalization | 42 (26.7–76.0) | 46.5 (28–77) | 0.417 |
| Duration of polymyxins (days), median (IQR) | 12 87 – 16) | 12 (7–16) | 0.645 |
| Baseline serum albumin, g/dL, median (IQR) | 2.5 (2.2–2.8) | | 0.062 |
| Baseline serum creatinine, mg/dL, median (IQR) | 0.6 (0.4–0.88) | 0.6 (0.45–0.8) | 0.920 |
| **Concurrent drugs** | | | |
| At least one nephrotoxic drug | 117 (68.8) | 76 (63.3) | 0.329 |
| At least two nephrotoxic drug | 39 (22.9) | 25 (20.8) | 0.670 |
| Diuretics | 90 (52.9) | 58 (48.3) | 0.439 |
| Contrast agents | 28 (16.5) | 16 (13.3) | 0.463 |
| ACEI/ARBs* | 10 (5.9) | 3 (2.5) | 0.170 |
| NSAIDs* | 12 (7.1) | 5 (4.2) | 0.302 |
| Vasoactive agents | 66 (38.8) | 35 (29.2) | 0.089 |
| Vancomycin | 1 (0.6) | 1 (0.8) | 0.804 |
| Aminoglycosides | 2 (1.2) | 2 (1.7) | 1.000 |
| Voriconazole | 4 (2.4) | 9 (7.5) | **0.037** |
| Amphotericin B | 11 (6.5) | 5 (4.2) | 0.397 |
| Tacrolimus/sirolimus | 2 (1.2) | 1 (0.8) | 1.000 |
| **Comorbid diseases and conditions** | | | |
| Malignancy | 74 (43.5) | 54 (45.0) | 0.804 |
| Hypertension | 74 (43.5) | 42 (35.0) | 0.144 |
| Cardiovascular diseases | 56 (32.9) | 36 (30.0) | 0.596 |
| Chronic neurological disease | 51 (30.0) | 29 (24.2) | 0.274 |
| Diabetes mellitus | 42 (24.7) | 30 (25.0) | 0.954 |
| Chronic obstructive pulmonary disease | 26 (15.3) | 19 (15.8) | 0.091 |
| Charlson comorbidity score, median (IQR) | 5 (3–7) | 4.5 (3–6) | 0.149 |
| **Source of infection** | | | |
| Pneumonia | 72 (42.4) | 51 (42.5) | 0.980 |
| Bloodstream | 30 (17.6) | 24 (20.0) | 0.612 |
| Urinary tract | **2 (1.2)** | **15 (12.5)** | **< 0.001** |
| Intraabdominal | 6 (3.5) | 2 (1.7) | 0.340 |
| Soft tissue infection | 17 (10.0) | 9 (7.5) | 0.463 |
| Sepsis of unknown origin | 43 (25.3) | 19 (15.8) | 0.053 |
| **Causative microorganism** | | | |
| *Acinetobacter baumanni* | 65 (38.2) | 54 (45.0) | 0.249 |
| *Klebsiella pneumoniae* | 30 (17.6) | 21 (17.6) | 0.974 |
| *Pseudomonas* spp. | 18 (10.6) | 19 (15.8) | 0.187 |
| Empirically | 51 (30) | 21 (17.5) | 0.015 |

* ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, NSAID: Non-steroid anti-inflammatory drug

polymyxin therapy was very common, however, there is no difference between polymyxin B and CMS regarding nephrotoxicity. Older age, higher baseline serum creatinine and the use of at least two nephrotoxic agents are the factors associated with nephrotoxicity during polymyxin therapy. 40% of nephrotoxicity events were severe (Stage 3), 41.1% of patients needed withdrawal of the drug and 16% needed hemodialysis after polymyxin therapy. The reversal of nephrotoxicity was high after the discontinuation of polymyxin therapy. Septic shock, mechanical ventilation, presence of a central venous catheter and Charlson comorbidity index were the independent predictors of mortality. The type of polymyxin was not related to mortality.

Neurotoxicity is a significant adverse effect of polymyxins. Paresthesia is the most frequently experienced adverse event and older studies reported incident rates between 7.3% and 27% [6, 9]. Nevertheless, neurotoxicity

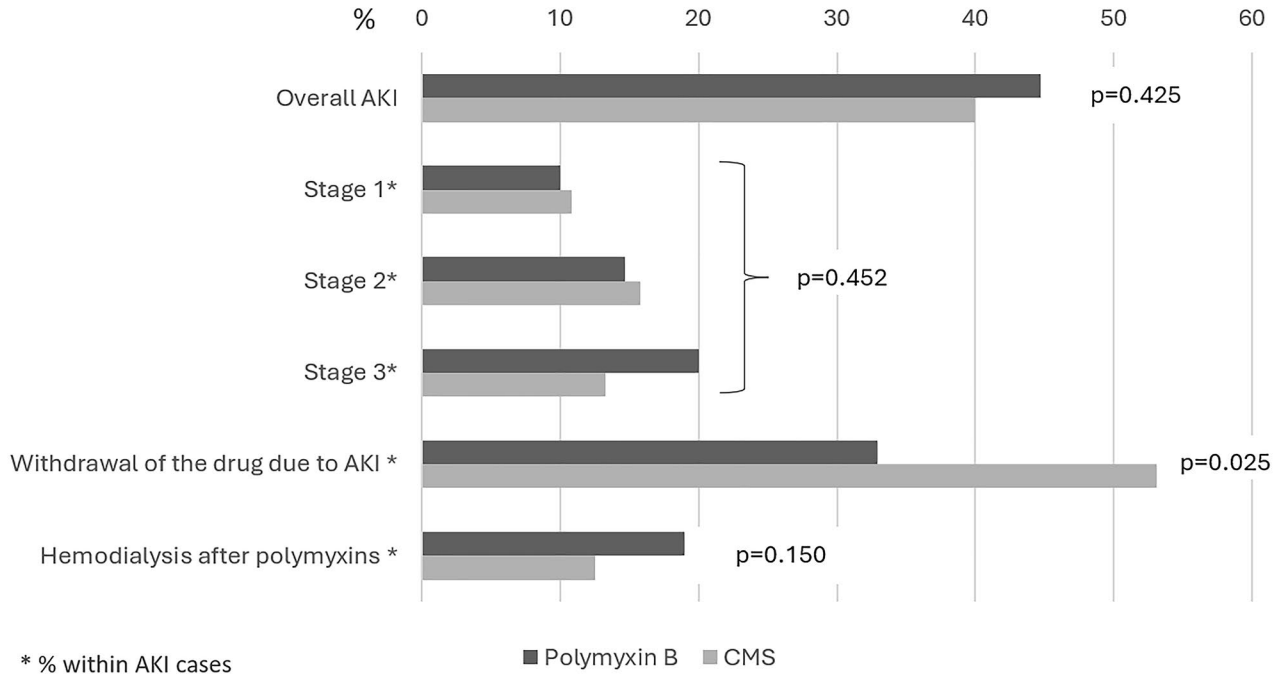


**Fig. 2** Parameters related to nephrotoxicity

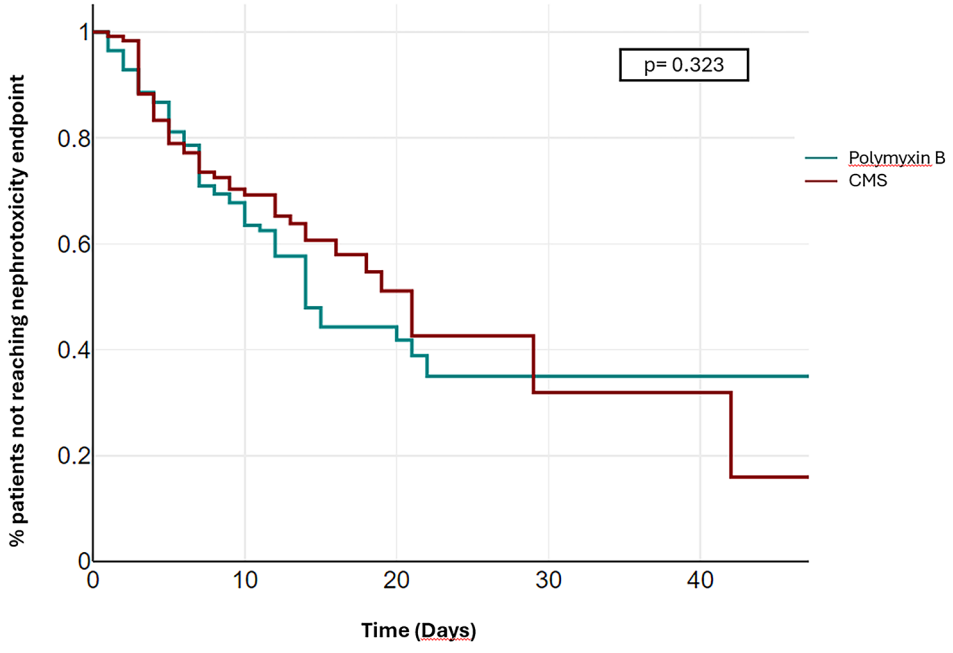


**Fig. 3** Comparison of the onset of nephrotoxicity (Log-rank test, $p = 0.323$)

is less reported in the recent literature and there is not enough data to truly evaluate the incidence [10]. Current studies mainly include critical patients who are sedated or unresponsive, therefore, the neurotoxic effects might be unreported. Furthermore, symptoms associated with neurotoxicity might be missed due to the lack of objective criteria. Recently, Liu et al. investigated the adverse effects of polymyxin B in healthy Chinese subjects and revealed that 7 of 10 subjects who received polymyxin B at 0.75 mg/kg dose and all 10 subjects who received 1.5 mg/kg dose had various neurotoxic events [11]. In our study, we just considered conscious patients

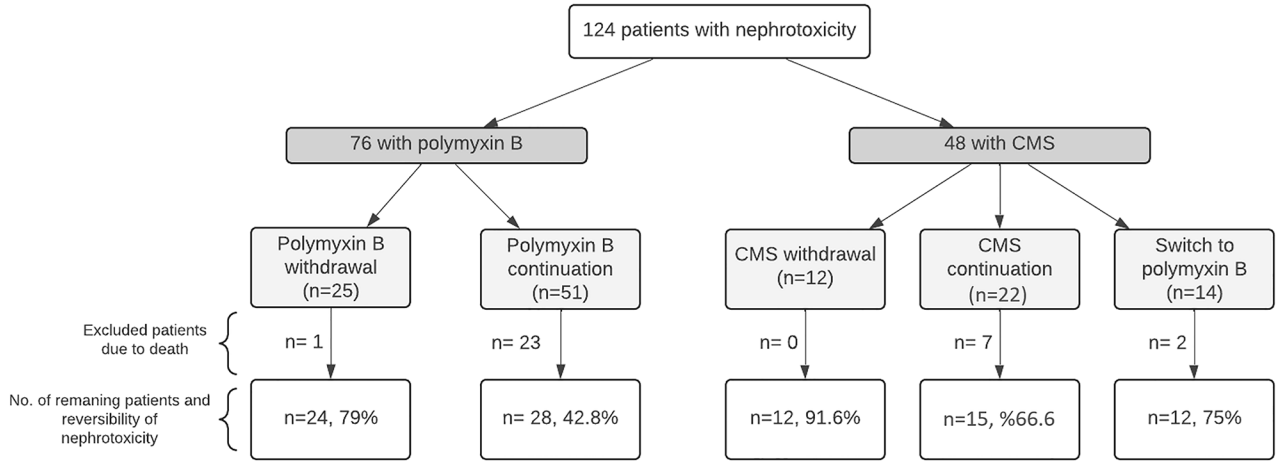


**Fig. 4** The details of patients with nephrotoxicity reversal

**Table 3** Univariate and multivariate analyses of factors associated with AKI

| **All patients (*n*)** | **Univariate analysis** | | | **Multivariate analysis** | |
|---|---|---|---|---|---|
| | **AKI (+) *n* = 124 (%)** | **AKI (-) *n* = 166 (%)** | ***P* value** | **Adjusted OR (95%CI)** | ***P* value** |
| Age, median (IQR) | 69 (61–78) | 61.5 (49.7–70.0) | **< 0.001** | 1.05 (1.02–1.07) | **< 0.001** |
| Gender, male | 77 (62.1) | 107 (64.5) | 0.680 | | |
| ICU | 90 (72.6) | 121 (72.9) | 0.953 | | |
| Septic shock | 35 (28.2) | 45 (27.1) | 0.833 | | |
| Duration of therapy (days), median (IQR) | 12 (8–18) | 12 (7–16) | 0.318 | | |
| Polymyxin B | 76 (61.3) | 94 (56.6) | 0.425 | | |
| CMS | 48 (38.7) | 72 (43.3) | | | |
| Applied loading dose | 118 (95.2) | 157 (94.6) | 0.824 | | |
| Baseline serum albumin, g/dL, median (IQR) | 2.5 (2.2–2.8) | 2.6 (2.3–2.9) | 0.076 | | |
| Baseline serum creatinine, mg/dL, median (IQR) | 0.7 (0.6–0.9) | 0.5 (0.4-07) | **< 0.001** | 2.99 (1.17–7.64) | **0.022** |
| **Concurrent drugs** | | | | | |
| At least one nephrotoxic drug (except polymyxins) | 87 (70.2) | 106 (63.9) | 0.260 | | |
| At least two nephrotoxic drugs (except polymyxins) | 36 (29.0) | 28 (16.9) | **0.013** | 2.45 (1.29–4.65) | **0.006** |
| Diuretics | 75 (60.5) | 73 (44.0) | **0.005** | | |
| Contrast agents | 17 (13.1) | 27 (16.3) | 0.548 | | |
| ACEI/ARBs* | 4 (3.2) | 9 (5.4) | 0.371 | | |
| NSAIDs* | 6 (4.8) | 11 (6.6) | 0.521 | | |
| Vasoactive agents | 53 (42.7) | 48 (28.9) | **0.014** | | |
| Voriconazole | 5 (4.0) | 8 (4.8) | 0.749 | | |
| Amphotericin B | 11 (8.9) | 5 (3.0) | **0.031** | 2.91 (0.85–9.97) | 0.087 |
| **Comorbid diseases** | | | | | |
| Malignancy | 55 (44.4) | 73 (44.0) | 0.949 | | |
| Hypertension | 57 (46.0) | 59 (35.5) | 0.073 | | |
| Cardiovascular disease | 51 (41.1) | 41 (24.7) | **0.003** | | |
| Diabetes mellitus | 30 (24.2) | 43 (25.3) | 0.829 | | |
| Charlson comorbidity score, median (IQR) | 5 (4–6) | 4 (2–7) | 0.055 | 0.91 (0.82–1.01) | 0.096 |

*ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, NSAID: Non-steroid anti-inflammatory drug

who can express their neurological findings during polymyxin therapy and found that 9.5% of patients receiving polymyxins had neurological symptoms. Nearly all neurotoxic events in our study were associated with polymyxin B and paresthesia was the main symptom. Most events occurred within the first 72 h of drug initiation. Neurotoxicity seems to be unrelated to nephrotoxicity, only a patient in our cohort experienced nephrotoxicity and neurotoxicity at the same time. Furthermore, all adverse events were reversible after the drug withdrawal.

**Table 4** Univariate and multivariate analyses of factors associated with mortality

| | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | **30-day mortality (+) n = 231 (%)** | **30-day mortality (-) n = 182 (%)** | **p** | **Adjusted OR (95%CI)** | ***P* value** |
| Age, median (IQR) | 69 (60–80) | 64.5 (52.7–73.2) | **< 0.001** | | |
| Gender, male | 142 (54.8) | 117 (45.2) | 0.509 | | |
| Intensive care unit admission | 205 (64.1) | 115 (35.9) | **< 0.001** | | |
| Septic shock | 120 (77.4) | 35 (22.6) | **< 0.001** | 2.20 (1.30–3.71) | **0.003** |
| Mechanical ventilation | 199 (70.1) | 85 (29.9) | **< 0.001** | 3.38 (1.87–6.11) | **< 0.001** |
| Presence of a central venous catheter | 204 (68.0) | 96 (32.0) | **< 0.001** | 2.36 (1.26–4.41) | **0.007** |
| Baseline serum albumin, g/dL, median (IQR) | 2.4 (2.2–2.6) | 2.6 (2.4–2.9) | **< 0.001** | | |
| Baseline serum creatinine, mg/dL, median (IQR) | 1.1 (0.6–1.9) | 0.7 (0.4–1.1) | **< 0.001** | | |
| Type of polymyxin | | | | | |
| Polymyxin B | 158 (60.3) | 104 (39.7) | **0.018** | | |
| Colistin | 73 (48.3) | 78 (51.7) | | | |
| **Comorbid diseases and conditions** | | | | | |
| Malignancy | 112 (65.9) | 58 (34.1) | 0.001 | | |
| Chronic kidney disease | 49 (75.4) | 16 (24.6) | 0.001 | | |
| Hypertension | 117 (58.8) | 82 (41.2) | 0.281 | | |
| Cardiovascular diseases | 98 (63.6) | 56 (36.4) | 0.017 | | |
| Chronic neurological disease | 60 (52.6) | 54 (47.4) | 0.473 | | |
| Diabetes mellitus | 72 (60.5) | 47 (39.5) | 0.281 | | |
| Chronic obstructive pulmonary disease | 35 (56.5) | 27 (43.5) | 0.527 | | |
| Charlson comorbidity score, median (IQR) | 6 (4–8) | 4 (2–6) | **< 0.001** | 1.21 (1.11–1.32) | **< 0.001** |
| **Source of infection** | | | | | |
| Pneumonia | 94 (59.9) | 63 (40.1) | 0.222 | | |
| Bloodstream | 56 (65.1) | 30 (34.9) | 0.057 | | |
| Urinary tract | **6 (26.1)** | **17 (73.9)** | **0.003** | | |
| Intraabdominal | 7 (53.8) | 6 (46.2) | 0.870 | | |
| Soft tissue infection | 13 (40.6) | 19 (59.4) | 0.067 | | |
| Sepsis of unknown origin | 55 (54.5) | 46 (35.5) | 0.731 | | |
| **Causative microorganism** | | | | | |
| *Acinetobacter baumanni* | 93 (57.4) | 69 (42.6) | 0.659 | | |
| *Klebsiella pneumoniae* | 42 (56.8) | 32 (43.2) | 0.895 | | |
| *Pseudomonas* spp. | 22 (50.0) | 22 (50.0) | 0.391 | | |

Patients with neurotoxicity were younger than the whole population and there wasn't a gender preference. John et al. investigated infusion-related adverse events in patients receiving polymyxin B at doses exceeding 3 mg/kg or 250 mg/day and reported a 3.9% neurotoxicity incidence in patients not receiving sedatives [12]. They also reported that patients with neurotoxicity were relatively young, had low Charlson comorbidity scores and better renal functions than patients without neurotoxicity. Similar to John et al.'s study, 11 of 14 patients in our study had good renal functions and the median Charlson comorbidity score was lower than the entire cohort. In contrast to their study, none of our patients were administered doses higher than 2.5 mg/kg/day and total daily doses were ≤ 200 mg in all patients.

The prevalence of nephrotoxicity associated with polymyxins has an increasing trend through the years and reaches up to 74% in colistin-treated patients and 46% in polymyxin B-treated patients in the literature [13]. The cumulative prevalence of nephrotoxicity induced by polymyxins is 30.3–45% in current meta-analyses [14–16]. The cumulative rate of nephrotoxicity in our study was 42.8% (44.7% for polymyxin B and 40.0% for CMS) and nephrotoxicity occurred median 6th days of therapy. A majority of patients in our cohort were critical care patients and one-third had septic shock, therefore, these high nephrotoxicity rates are not surprising. In the literature, newer studies have reported higher nephrotoxicity rates than older studies. Oliota et al. mentioned that assessing nephrotoxicity by standardized criteria such as RIFLE, AKIN and KDIGO has increased the sensitivity of nephrotoxicity associated with polymyxins and led to an increase in these rates annually after 2009 [14]. In this study, we used internationally recognized KDIGO criteria to both diagnose and classify AKI, which also may lead to a high nephrotoxicity rate.

In the literature, there is an ongoing debate on whether colistin or polymyxin B therapy induces more

nephrotoxicity. Colistin is generally thought to have an increased potential to cause nephrotoxicity than polymyxin B [17]. The toxic effect of polymyxins on renal tubular cells is a well-known phenomenon. It is suggested that the differences in pharmacokinetics and renal handling mechanisms between polymyxins may lead to higher colistin toxicity in humans [4]. However, many observational studies have shown variable rates of nephrotoxicity due to polymyxins. Meta-analyses either have conflicting data. In Sisay et al.'s meta-analysis, including 48 studies conducted using RIFLE criteria for AKI, colistin had a 37% increased risk of developing nephrotoxicity compared to polymyxin B [16]. In contrast to this study, another larger meta-analysis showed that the pooled prevalence of colistin-induced nephrotoxicity was not higher than that of polymyxin B-induced nephrotoxicity [14]. Wagenlehner et al. demonstrated that no significant difference in rates of nephrotoxicity assessed by internationally recognized criteria between patients treated with systemic colistin and polymyxin B in the subgroup analysis of their meta-analysis although a pairwise analysis of comparative studies showed a lower rate of nephrotoxicity with polymyxin B [18]. In our study, we couldn't find any difference in AKI rates of polymyxins. Besides, the nephrotoxicity rate, the stages of AKI and hemodialysis required after polymyxin therapy were similar between groups. Although not statistically significant, AKI seems to occur earlier with CMS than with polymyxin B. When AKI occurred, polymyxin therapy was discontinued in only less than half of the patients, probably due to the lack of alternative antibiotic therapy for carbapenem-resistant microorganisms which are very prevalent in our setting. Our data show that clinicians were more likely to discontinue CMS than polymyxin. Besides some clinicians preferred to switch the CMS to polymyxin B. The reasons for that can be the belief that polymyxin B is less nephrotoxic than CMS, and also there is no renal dose adjustment for polymyxin B which provides ease of use. Nephrotoxicity reversed in the majority of patients after drug withdrawal. Nephrotoxicity was reversible for many patients even if the polymyxin therapy was not discontinued. Hydration, dose modifications for CMS, and discontinuation of the other nephrotoxic drugs may be responsible for the reversal of AKI for these patients.

Predictors of polymyxin-induced nephrotoxicity were widely investigated in the literature. Older age, the concomitant use of other nephrotoxic drugs such as vasopressors and diuretics, underlying diabetes mellitus, higher polymyxin doses, longer duration of therapy, baseline serum creatinine, presence of sepsis/septic shock were the main factors independently associated with nephrotoxicity in several studies [13, 15, 16]. Patients with high serum albumin and high glomerular filtration rate at baseline were less likely to experience nephrotoxicity [15, 16]. Concerning the mechanism of hypoalbuminemia, it is hypothesized that patients with low albumin levels may have higher serum levels of free colistin because the medication is 50% protein bound and preferentially binds to albumin. This might result in the accumulation of more drug in kidney tubular cells, enhancing the risk of nephrotoxicity. Moreover, hypoalbuminemia per se may also reflect the severity of the underlying illness. Our data show that older age, higher baseline serum creatinine and the use of at least two nephrotoxic agents were independent predictors of polymyxin-induced nephrotoxicity, compatible with the literature.

There are several clinical PK differences between colistin and polymyxin B beyond their similar antimicrobial spectrum of activity. Although polymyxin B is known to have several PK advantages over colistin, better clinical efficacy or less mortality was not observed with it in many studies. In a prospective multicenter study, the 30-day mortality was 30.9% in colistin and 43.4% in polymyxin B groups and the difference was not statistically different [19]. In a recent retrospective cohort study, polymyxin B or colistin treatment did not impact 30-day mortality in patients with carbapenem-resistant *A. baumannii* or *P. aeruginosa* bloodstream infections [20]. Vardakas et al. also demonstrated similar 30-day mortality rates in their meta-analysis [13]. Our multivariate analysis also showed that the type of polymyxin was not related to mortality. Septic shock, mechanical ventilation, presence of a central venous catheter and Charlson comorbidity index were the independent predictors of mortality.

Our study has some limitations. Symptoms associated with neurotoxicity were mainly evaluated by consultant infectious diseases doctors in most patients and neurology consultation was not available. Neurotoxicity assessment was subjective and did not depend on any standardized criteria so less severe symptoms may have been ignored and not recorded. Considering these factors and the retrospective nature of this study, we may have underreported neurological adverse events. Literature supports that polymyxin-induced nephrotoxicity is dose-dependent and AKI risk increases if they are administered in higher doses. In our study, we administered similar loading and maintenance doses in all patients for both polymyxins as suggested in "International Consensus Guidelines for the Optimal Use of the Polymyxins. Therefore, we could not assess the effect of dosing regimens on the risk of polymyxin nephrotoxicity.

## Conclusion

Our study presents data on polymyxin-associated neurotoxicity which is scarce in the literature, and a detailed comparison of nephrotoxicity. Neurotoxicity is a reversible but relatively common adverse event that leads to

drug withdrawal during the use of polymyxins, particularly polymyxin B. Nephrotoxicity is very common during polymyxin therapy and its frequency is similar between the two polymyxins. It leads to drug discontinuation in many patients, however, it is mostly reversible after the discontinuation of the polymyxin therapy. Older age, higher baseline creatinine and the use of at least two nephrotoxic agents, but not the type of polymyxin, are associated with AKI in patients on polymyxin therapy. The type of polymyxin was not associated with mortality for infections caused by MDR Gram-negative bacteria. Both polymyxins can be preferred in clinical practice with close monitoring for AKI.

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**Author contributions**
We declare that all authors meet the ICMJE authorship criteria.PAY, ÖÖT and MD were responsible for the design of the study. AFŞ, ÖÖT, SK were responsible for data acquisition. PAY and HSÖ were responsible for data analysis, interpretation and statistical analyses. PAY, ÖÖT, AFŞ and SK were responsible for writing the draft. HSÖ and MD reviewed the draft. All authors contributed to the writing of the final manuscript. All authors approved the final version of the manuscript.

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**Data availability**
Our dataset is not available online. However, the dataset used and analysed during the current study is available from the corresponding author on request.

## Declarations

**Competing interests**
The authors declare no competing interests.

**Ethics approval and consent to participate**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Gazi University Ethics Committee with decision number 11, on June 6, 2023.

**Informed consent**
Informed consent to participate was waived by Gazi University Ethics Committee due to the retrospective nature of the study.

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