International Journal of Infectious Diseases 117 (2022) 37–44

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

# Risk factors for polymyxin B-associated acute kidney injury

Kang Chang[1], Haibo Wang[2], Jianping Zhao[3], Xianghong Yang[4], Bo Wu[5], Wenkui Sun[6], Man Huang[7], Zhenshun Cheng[8], Hong Chen[9], Yuanlin Song[10], Ping Chen[11], Xiangqi Chen[12], Xin Gan[13], Wanli Ma[14], Lihua Xing[15], Yimin Wang[16,*], Bin Cao[1,17,**]

[1] China-Japan Friendship Hospital, National Clinical Research Center for Respiratory Diseases, Clinical Center for Pulmonary Infections, Capital Medical University, Beijing, 100029, China
[2] Peking University Clinical Research Institute, Peking University First Hospital, 38 Xueyuan Rd, Haidian District, Beijing, 100191, China
[3] Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Sciences & Technology, Wuhan, 430030, China
[4] Department of Intensive Care Unit, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, 310014, China
[5] Department of Respiratory and Critical Care Medicine, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, 214023, China
[6] Department of Respirology and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, China
[7] Department of General Intensive Care Unit, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, 310052, China
[8] Department of Pulmonary and Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, 430062, China
[9] Department of Respiratory and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200025, China
[10] Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, 201799, China
[11] Department of Respiratory Medicine, The Second Xiangya Hospital, Central South University, Changsha, 410012, China
[12] Departments of Respiratory Medicine, Fujian Medical University Union Hospital, Fujian Medical University, Fuzhou, 350001, China
[13] Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, 330006, China
[14] Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China
[15] Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China
[16] Department of Pulmonary and Critical Care Medicine, China Centre of Respiratory Medicine, National Clinical Research Centre for Respiratory Diseases, China-Japan Friendship Hospital, Institute of Respiratory Medicine, Beijing, 100029, China
[17] Department of Pulmonary and Critical Care Medicine, China Centre of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, China-Japan Friendship Hospital; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Peking Union Medical College; Department of Respiratory Medicine, Capital Medical University; Tsinghua University School of Medicine, Beijing, 100029, China

ARTICLE INFO

*Article history:*
Received 16 December 2021
Revised 25 January 2022
Accepted 26 January 2022

*Keywords:*
Polymyxin B
Nephrotoxicity
Acute kidney injury
Carbapenem-resistant organism
Risk factors

ABSTRACT

*Objectives:* This study aimed to assess the current incidence and risk factors for polymyxin B-associated acute kidney injury (AKI) in Chinese hospitals for a more effective clinical use for polymyxin B.
*Methods:* This multicenter, retrospective cohort study included patients from 14 Chinese teaching hospitals who received polymyxin B therapy. Univariate and multivariate logistic regression models were used to determine the factors associated with polymyxin B-associated incident AKI. Furthermore, a multivariate logistic regression model was used to identify the independent risk factors for AKI.
*Results:* A total of 251 patients were included in the analysis. The overall incidence of AKI was 33.5%. A multivariate logistic regression model identified the loading dose (hazard ratio (HR), 1.84; 95% confidence interval (CI), 1.01–3.38; P = 0.0491) and the use of two or more nephrotoxic drugs (HR, 3.56; 95% CI, 1.55–8.18; P = 0.0029) as independent risk factors for the occurrence of AKI. Meanwhile, the estimated glomerular filtration rate had a protective effect (HR, 0.99; 95% CI, 0.98–0.99; P = 0.0006) on the occurrence of AKI. The daily dose, cumulative dose, and treatment duration of polymyxin B did not affect the occurrence of AKI.

* Corresponding authors: Yimin Wang, Department of Pulmonary and Critical Care Medicine, China Centre of Respiratory Medicine, National Clinical Research Centre for Respiratory Diseases, China-Japan Friendship Hospital, Institute of Respiratory Medicine, No. 2 East Yinghua Road, Chaoyang District, Beijing, 100029, China, Phone: +86-010-84206269.
** Bin Cao: Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, No. 2 East Yinghua Road, Chaoyang District, Beijing, 100029, China, Phone: +86-010-84206257.
*E-mail addresses:* wymderek@163.com (Y. Wang), caobin_ben@163.com (B. Cao).

https://doi.org/10.1016/j.ijid.2022.01.055

*Conclusions:* The use of polymyxin B loading doses and the combined use of multiple nephrotoxic drugs are independent risk factors for polymyxin B-associated AKI. The severity of AKI may be higher in patients with elevated baseline creatinine levels.



## Introduction

Nephrotoxicity is an important factor in evaluating the clinical effectiveness of polymyxins. When polymyxins had just been used in the clinics, the incidence of adverse events was very high, especially nephrotoxicity and neurotoxicity; although the definition of nephrotoxicity is not well established, studies have reported that its incidence was as high as 10%–50% (Falagas and Kasiakou, 2006). The high incidence of nephrotoxicity and the emergence of new antibiotics with low toxicity (such as aminoglycosides and second-generation and third-generation cephalosporins) have resulted in fewer polymyxins being used in the clinic since the 1970s.

Currently, many studies are evaluating polymyxin-associated nephrotoxicity, and more than 80% of them are specific to colistin. Kvitko et al. (2011) found that 36% (16/45) of patients receiving polymyxin B for treating bacteremia caused by *Pseudomonas aeruginosa* infection developed nephrotoxicity compared with only 11% (10/88) of patients that developed the same condition upon receiving other antibiotics ($P = 0.002$). In another study, Paul et al. (2010) compared the incidence of nephrotoxicity after treatment with colistin or other antibiotics for infections with *P. aeruginosa, Acinetobacter baumannii*, or Enterobacteriaceae; they found that when the former was used, nephrotoxicity's incidence was 16% (26/128) compared with only 7% (17/244) in the control group ($P = 0.006$). However, the incidence of polymyxin B-related nephrotoxicity reported in the literature varies widely, ranging from as low as 4% (Ramasubban et al. 2008) to as high as 60% (Kubin et al. 2012). The main reasons for such inconsistent findings across these studies are the differences in the dosage of polymyxins and disparate definitions of nephrotoxicity. For example, studies using the RIELF (Risk, Injury, Failure, Loss, and End-stage kidney disease) nephrotoxicity criteria reported a 39% (122/330) incidence of nephrotoxicity (Esaian et al. 2012; Kubin et al. 2012; Akajagbor et al. 2013; Phe et al. 2014), while those using other criteria reported a 17% (16/96) incidence (Ouderkirk et al. 2003; Sobieszczyk et al. 2004; Oliveira et al. 2009). Noteworthy, the most commonly used nephrotoxicity criteria in published clinical studies are the RIELF criteria. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria for diagnostic were introduced later, and some studies have shown that more patients with AKI can be identified using the KDIGO criteria (Zhou et al. 2016).

Due to the continuous increase in carbapenem-resistant organisms, polymyxins (including colistin and polymyxin B) were reintroduced into clinical practice in 1990s. However, the nephrotoxicity of polymyxins remained a concern for the clinicians. Polymyxin B entered the Chinese market at the end of 2017, and since then, its irregular use has become very common (such as no loading dose, low maintenance dose, etc.). Therefore, this study aimed to assess the current incidence and risk factors of polymyxin B-related nephrotoxicity in Chinese hospitals in order to guide the clinicians toward a more effective utilization of polymyxin B.

## Methods

### *Study design*

This multicenter, retrospective cohort study was conducted from January 2018 to May 2020 in 14 Chinese teaching hospitals to evaluate the incidence and risk factors of polymyxin B-associated AKI. The study protocol was approved by the ethics committee of the China-Japan Friendship Hospital (No. 2018-146-K103) without the need of written informed consents. The other hospitals accepted the approval by the ethics committee of the China-Japan Friendship Hospital. The study was carried out in accordance with the Declaration of Helsinki. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

### *Patient selection criteria*

Adult patients (≥18 years) diagnosed with hospital-acquired pneumonia (HAP) due to carbapenem-resistant *A. baumannii* (CRAB) or carbapenem-resistant Enterobacteriaceae who received intravenous polymyxin B were included in this study. The patients were divided into two groups based on the presence and absence of AKI: the AKI group and non-AKI group. Patients with AKI at the time of HAP diagnosis and those who died within 48 h of polymyxin B use were excluded from this study.

### *Study variables definitions*

The primary outcome of this study was the occurrence of AKI during hospitalization. The definition and staging of AKI were based on the KDIGO standards (Khwaja, 2012). All potential confounding variables were collected, including demographics, underlying conditions, Charlson comorbidity index (Charlson et al. 1987), mechanical ventilation, laboratory tests, acute physiology and chronic health evaluation II score (Knaus et al. 1985), sequential organ failure assessment score (Vincent et al. 1996), microbiological data, characteristics of polymyxin B use, and concomitant nephrotoxins. HAP was defined as new pneumonia (a lower respiratory tract infection verified by the presence of a new pulmonary infiltrate on imaging) that developed more than 48 h after admission in nonintubated patients (Modi and Kovacs, 2020). The polymyxin B loading dose was defined as the first dose exceeding the maintenance dose. The definition of ideal body weight was as previously described (Lee et al. 2015). The estimated glomerular filtration rate (eGFR) was calculated according to a previous formula (Teo et al. 2011).

### *Statistical analysis*

SAS software (version 9.4, SAS Institute, Cary, NC, United States) was used for all statistical analyses. The baseline characteristics were compared between the two groups using chi-square or Fisher exact test for categorical variables, and Student t-test or Wilcoxon rank sum test for continuous variables, as appropriate. Analysis of variance or Kruskal–Wallis H test was used to compare differences among participants with different severities of AKI. Univariate and multivariate logistic regression models were used to determine the factors associated with polymyxin B-associated incident AKI, and the association between related factors and incident AKI was presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables that were significant in the univariate analysis were included in a stepwise multivariate logistic regression model with an

entry criterion of P < 0.20 and an exit criterion of P > 0.05. All P values were two-sided and P < 0.05 was considered statistically significant.

## Results

### *Baseline characteristics of patients*

A total of 251 patients were included in this study for analysis. There were 84 patients in the AKI group and 167 patients in the non-AKI group. The demographic and clinical information of these patients is summarized in Table 1. The overall incidence of AKI was 33.5% (84/251), and a total of 176 (70.1%) patients were male. The most common bacteria isolated were carbapenem-resistant *A. baumannii* (136/251; 64.9%) and carbapenem-resistant *Klebsiella pneumoniae* (153/251; 60.9%). Of all the patients, 67.3% (169/251) had infection from more than one pathogen, and 27 patients had a history of chronic kidney disease (CKD). There was no significant difference between the AKI and non-AKI groups in terms of baseline serum creatinine levels (66.30 ± 29.70 vs 61.65 ± 36.60; P = 0.0552). Furthermore, there were no significant differences in disease severity between the two groups, namely in terms of the SOFA (sequential organ failure assessment) (6.25 ± 3.42 vs 5.68 ± 3.18; P = 0.1946) and APACHE II (acute physiology and chronic health evaluation II score) (16.61 ± 6.07 vs 16.98 ± 7.00; P = 0.6811) scores. In addition, the sepsis biomarkers procalcitonin and C-reactive protein were also not found to differ statistically between the two groups. However, the AKI group showed lower eGFR and higher creatinine levels when HAP was diagnosed, despite being within the normal range (94.90 ± 35.19 vs 112.55 ± 39.66; P = 0.0008; 71.50 ± 42.00 vs 57.95 ± 40.80; P = 0.0008, respectively). In the AKI group, the proportion of patients whose daily exposure dose exceeded the recommended dose was higher than that in the non-AKI group (14.3% vs 4.2%). The drug use rate and number of nephrotoxic drugs in the AKI group were also significantly higher than those in the non-AKI group.

### *Risk factors related to the occurrence of AKI*

The risk factors associated with the occurrence of AKI are listed in Table 2. In the multivariate analysis, only three variables (eGFR, loading dose, and use of two or more nephrotoxic drugs) showed an independent correlation with the occurrence of AKI after adjusting for underlying confounders. Among them, eGFR had a protective effect (HR, 0.99; 95% CI, 0.98–0.99; P = 0.0006) on the occurrence of AKI. The loading dose (HR, 1.84; 95% CI, 1.01–3.38; P = 0.0491) and the use of two or more nephrotoxic drugs (HR, 3.56; 95% CI, 1.55–8.18; P = 0.0029) were independent risk factors for AKI. Notably, the analysis results showed that some factors of concern such as the daily dose/actual body weight, cumulative dose, and treatment duration did not affect the occurrence of AKI.

### *Risk factors related to the severity of AKI*

The risk factors associated with the severity of AKI are listed in Table 3. We found that patients with higher baseline creatinine levels may have more severe AKI. Whether the patient had CKD in the past and the severity of the disease were not directly related to the severity of AKI.

## Discussion

This study is the largest clinical study on polymyxin B-associated AKI since the launch of polymyxin B in China. This study retrospectively summarized the association between the use of polymyxin B and the incidence of nephrotoxicity after the former entered the Chinese market. We found that the loading dose of polymyxin B and the combined use of multiple nephrotoxic drugs were independent risk factors for the occurrence of AKI, and the dosage and duration of polymyxin B were not significantly correlated with the occurrence of nephrotoxicity.

Recent pharmacokinetic data emphasize the importance of the loading dose, as it can reach the target serum concentration quickly. Some data indicated that a loading dose of 2–2.5 mg/kg could help patients achieve a steady-state serum concentration of polymyxin B faster (Sandri et al. 2013). Clinicians are extremely concerned about whether the loading dose may affect kidney function. However, to date, studies exploring the safety (and effectiveness) of polymyxin loading doses are very limited, and conclusions have been inconsistent. After analyzing 81 patients with colistin, Rigatto found that 17 of 22 patients (77%) who received the loading dose developed renal failure, whereas only 14 of 59 patients (24%) who did not receive the loading dose developed renal failure (P < 0.001) (Rigatto et al. 2016). It is worth mentioning that there were significant baseline differences between patients receiving and patients not receiving a loading dose, including baseline renal function and chronic comorbidities. However, when these different variables were controlled and analyzed, it was found that colistin loading dose was still associated with an increased risk for AKI (HR, 5.2; 95% CI, 2.3–12.0). Nelson found that the incidence of nephrotoxicity in patients who received a loading dose of polymyxin B (defined as the initial dose ≥ 2.5 mg/kg) was not associated with an increased risk for AKI (Nelson et al. 2015). In this study, the proportion of patients with AKI who received a loading dose was 9/19 (47%), whereas the proportion of patients who did not receive the loading dose was 30/90 (33%) (P = 0.3). Compared with the above studies, the advantage of the present study is that the sample size is larger and the loading dose has a clearer definition; therefore, the results may have more reference value.

The results of some in vitro studies also suggest that polymyxins have a concentration-dependent mechanism of nephrotoxicity. In vitro cell culture studies with rat NRK-52E and human HK-2 kidney tubular cells showed that after treatment with polymyxins, the cells undergo concentration-dependent and time-dependent apoptosis (Azad et al. 2013; Azad et al., 2015a). In NRK-52 cells, polymyxin B treatment caused concentration-dependent activation of caspase-3, caspase-8, and caspase-9, DNA damage, and translocation of membrane phosphatidylserine (Azad et al. 2013; Azad et al., 2015b). In addition, in NRK-52E cells, polymyxin B also caused concentration-dependent and time-dependent mitochondrial damage, including mitochondrial morphology from filamentous to fragmented, loss of mitochondrial membrane potential, and reactive oxygen species production (Azad et al., 2015b). We speculated that the use of polymyxin B loading doses may cause the renal tubular cells of patients to reabsorb a great amount of drugs in a short period of time and then induce renal tubular cell death through various mechanisms such as metabolism and inflammation perturbations, oxidative stress, cell cycle arrest, and apoptosis, which increases the patient's risk for AKI.

This study found that the combination of two or more nephrotoxic drugs is an independent risk factor related to the occurrence of AKI during the use of polymyxin B. However, multivariate analysis did not find that a specific drug would have an independent effect on the occurrence of AKI. Several studies reached similar conclusions. Pogue et al. found that combining three or more nephrotoxic drugs was an independent risk factor for colistin-related nephrotoxicity (odds ratio (OR), 6.80; 95% CI, 1.42–32.49) (Pogue et al. 2011). Mendes et al. found that the combined use of vasopressors was an independent risk factor for polymyxin B-related AKI (OR, 3.03; 95% CI, 1.02–9.04; P = 0.047) (Mendes et al. 2009). It reminds us that when polymyxin B is used clinically, caution should be exercised when using other drugs that

**Table 1**
Baseline characteristics based on the development of nephrotoxicity during polymyxin B therapy

| | AKI group (N = 84) | Non-AKI group (N = 167) | P value |
|---|---|---|---|
| Demographics | | | |
| Sex, male | 61 (72.6) | 115 (68.9) | 0.5395 |
| Age, years | 61.40 ± 16.71 | 54.98 ± 18.20 | 0.0071 |
| Actual body weight, kg | 65.69 ± 16.72 | 61.17 ± 11.34 | 0.0531 |
| Ideal body weight, kg | 50.31 ± 2.05 | 50.07 ± 2.16 | 0.4623 |
| Body mass index, kg/m$^2$ | 22.89 ± 5.04 | 21.74 ± 3.50 | 0.1085 |
| Charlson comorbidity index | 1.89 ± 2.05 | 2.13 ± 1.81 | 0.3586 |
| Concomitant diseases and background | | | |
| Chronic respiratory diseases[a] | 40 (47.6) | 92 (55.1) | 0.2633 |
| Chronic cardiovascular diseases[b] | 41 (48.8) | 69 (41.3) | 0.2590 |
| Diabetes | 17 (20.2) | 30 (18) | 0.6630 |
| Chronic kidney diseases[c] | 9 (10.7) | 19 (11.4) | 0.8749 |
| Base creatinine, $\mu$ mol/L[e] | 66.30 ± 29.70 | 61.65 ± 36.60 | 0.0552 |
| Severity at CRE/CRAB HAP diagnosis | | | |
| SOFA score | 6.25 ± 3.42 | 5.68 ± 3.18 | 0.1946 |
| APACHE II score | 16.61 ± 6.07 | 16.98 ± 7.00 | 0.6811 |
| Estimated glomerular filtration rate, mL/min/1.73 m$^2$ | 94.90 ± 35.19 | 112.55 ± 39.66 | 0.0008 |
| Serum creatinine, $\mu$ mol/L[e] | 71.50 ± 42.00 | 57.95 ± 40.80 | 0.0008 |
| Bilirubin, $\mu$ mol/L | 29.12 ± 55.21 | 26.35 ± 40.73 | 0.6886 |
| Albumin, g/L | 33.67 ± 6.64 | 32.13 ± 6.68 | 0.0955 |
| Procalcitonin, $\mu$g/L[e] | 0.85 ± 1.86 | 0.66 ± 2.72 | 0.7648 |
| C-reactive protein, mg/L[e] | 46.20 ± 94.30 | 75.00 ± 128.40 | 0.1862 |
| Neutrophil count, $10^9$/L | 11.10 ± 9.73 | 9.64 ± 5.54 | 0.2105 |
| Erythrocyte sedimentation rate, mm/h | 39.89 ± 29.41 | 49.12 ± 33.23 | 0.2890 |
| $PaO_2/FiO_2$ ratio | 221.97 ± 115.87 | 226.26 ± 143.27 | 0.8341 |
| Mechanical ventilation | 45 (68.2) | 88 (73.9) | 0.4031 |
| ICU admission | 80 (95.2) | 140 (83.8) | 0.0083 |
| Sepsis | 19 (22.6) | 32 (19.2) | 0.7931 |
| Sepsis shock | 30 (35.7) | 60 (35.9) | |
| Pathogens at CRE/CRAB HAP diagnosis | | | |
| Carbapenem-resistant *Klebsiella pneumoniae* | 56 (66.7) | 97 (58.1) | 0.1884 |
| Carbapenem-resistant *Escherichia coli* | 3 (3.6) | 9 (5.4) | 0.7557 |
| Other CRE | 13 (15.5) | 19 (11.4) | 0.3582 |
| CRAB | 57 (67.9) | 106 (63.5) | 0.4922 |
| Carbapenem-resistant *Pseudomonas aeruginosa* | 31 (36.9) | 47 (28.1) | 0.1570 |
| Number of pathogens ≥ 2 | 61 (72.6) | 108 (64.7) | 0.2052 |
| Use characteristics of polymyxin B | | | |
| Loading dose | 30 (35.7) | 42 (25.1) | 0.0808 |
| Cumulative dose, mg | 1427.44 ± 985.05 | 1419.49 ± 1064.42 | 0.9544 |
| Daily dose/actual body weight, mg/kg/d | 1.98 ± 1.12 | 1.89 ± 0.52 | 0.5159 |
| Daily dose/ideal body weight, mg/kg/d | 2.45 ± 1.21 | 2.22 ± 0.51 | 0.1299 |
| Daily dose/actual body weight < 2.5 mg/kg/d | 72 (85.7) | 151 (90.4) | 0.0537 |
| Daily dose/actual body weight > 3 mg/kg/d | 7 (8.3) | 3 (1.8) | |
| Daily dose/ideal body weight < 2.5 mg/kg/d | 65 (77.4) | 148 (88.6) | 0.0179 |
| Daily dose/ideal body weight > 3 mg/kg/d | 12 (14.3) | 7 (4.2) | |
| Frequency twice a day | 75 (89.3) | 148 (88.6) | 0.5215 |
| Frequency three times a day | 4 (4.8) | 13 (7.8) | |
| Treatment duration, d | 13.20 ± 10.81 | 13.14 ± 9.87 | 0.9622 |
| Highest serum creatinine concentration during hospitalization | 225.76 ± 125.32 | 107.81 ± 97.44 | <.0001 |
| Concomitant nephrotoxins | | | |
| Vancomycin | 34 (40.5) | 35 (21.0) | 0.0011 |
| Aminoglycosides[d] | 2 (2.4) | 0 (0.0) | 0.1111 |
| Amphotericin B | 15 (17.9) | 15 (9.0) | 0.0408 |
| Acyclovir | 0 (0.0) | 0 (0.0) | — |
| Vasopressor | 32 (38.1) | 43 (25.7) | 0.0437 |
| Methotrexate | 0 (0.0) | 0 (0.0) | — |
| Cis-platinum | 0 (0.0) | 0 (0.0) | — |
| Meropenem | 44 (52.4) | 92 (55.1) | 0.6844 |
| One nephrotoxic drug | 34 (40.5) | 63 (37.7) | 0.0166 |
| Receipt of ≥2 nephrotoxic drugs | 38 (45.2) | 54 (32.3) | |

APACHE, acute physiology and chronic health evaluation; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; $FiO_2$, fractional inspired oxygen; HAP, hospital-acquired pneumonia; ICU, intensive care unit; $PaO_2$, arterial oxygen partial pressure; SOFA, sequential organ failure assessment.
Data are presented as mean ± standard deviation or N (%), unless otherwise indicated.
[a] Chronic respiratory diseases included emphysema, chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung disease, chronic pulmonary hypertension, and pulmonary fibrosis.
[b] Chronic cardiovascular diseases included hypertension, coronary atherosclerotic heart disease, and congestive heart failure.
[c] Chronic kidney diseases included glomerulonephritis and nephrotic syndrome.
[d] Aminoglycosides included gentamicin, tobramycin, and amikacin.
[e] Data are presented as median ± interquartile range.

**Table 2**
Univariable and multivariable logistic regression analysis for independent risk factors for polymyxin B-associated nephrotoxicity in patients

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
| Demographics | | | | |
| Sex, male | 1.20 (0.67–2.14) | 0.5398 | | |
| Age, years | 1.02 (1.01–1.04) | 0.0082 | | |
| Actual body weight, kg | 1.03 (1.00–1.05) | 0.0415 | | |
| Ideal body weight, kg | 1.06 (0.91–1.22) | 0.4600 | | |
| Body mass index, kg/m$^2$ | 1.07 (0.99–1.16) | 0.0901 | | |
| Charlson comorbidity index | 0.93 (0.81–1.08) | 0.3585 | | |
| Concomitant diseases and background | | | | |
| Chronic respiratory diseases[a] | 0.74 (0.44–1.25) | 0.2639 | | |
| Chronic cardiovascular diseases[b] | 1.35 (0.80–2.29) | 0.2596 | | |
| Diabetes | 1.16 (0.60–2.25) | 0.6632 | | |
| Chronic kidney diseases[c] | 0.94 (0.40–2.17) | 0.8749 | | |
| Base creatinine, $\mu$ mol/L | 1.00 (1.00–1.01) | 0.088 | | |
| Severity at CRE/CRAB HAP diagnosis | | | | |
| SOFA score | 1.06 (0.97–1.14) | 0.1946 | | |
| APACHE II score | 0.99 (0.95–1.03) | 0.6797 | | |
| Mechanical ventilation | 0.76 (0.39–1.46) | 0.4038 | | |
| ICU admission | 3.86 (1.30–11.42) | 0.0148 | | |
| Estimated glomerular filtration rate, mL/min/1.73 m$^2$ | 0.99 (0.98–1.00) | 0.001 | 0.99 (0.98–0.99) | 0.0006 |
| Serum creatinine, $\mu$ mol/L | 1.01 (1.00–1.01) | 0.0642 | | |
| Bilirubin, $\mu$ mol/L | 1.00 (1.00–1.01) | 0.6583 | | |
| Albumin, g/L | 1.03 (0.99–1.08) | 0.0976 | | |
| Procalcitonin, $\mu$g/L | 0.98 (0.94–1.01) | 0.2016 | | |
| C-reactive protein, mg/L | 1.00 (0.99–1.00) | 0.2097 | | |
| Neutrophil count, 10$^9$/L | 1.03 (0.99–1.07) | 0.1625 | | |
| Prothrombin time, s | 0.95 (0.87–1.04) | 0.2886 | | |
| Activated partial thromboplastin time, s | 1.00 (0.98–1.02) | 0.7664 | | |
| Erythrocyte sedimentation rate, mm/h | 0.99 (0.97–1.01) | 0.2835 | | |
| $PaO_2/FiO_2$ ratio | 1.00 (1.00–1.00) | 0.8335 | | |
| Sepsis | 1.27 (0.64–2.55) | 0.4971 | | |
| Sepsis shock | 1.07 (0.59–1.94) | 0.8200 | | |
| Pathogens at CRE/CRAB HAP diagnosis | | | | |
| Carbapenem-resistant *Klebsiella pneumoniae* | 1.44 (0.83–2.50) | 0.1894 | | |
| Carbapenem-resistant *Escherichia coli* | 0.65 (0.17–2.47) | 0.5272 | | |
| Other CRE | 1.43 (0.67–3.05) | 0.3599 | | |
| CRAB | 1.22 (0.70–2.12) | 0.4924 | | |
| Carbapenem-resistant *Pseudomonas aeruginosa* | 1.49 (0.86–2.61) | 0.1581 | | |
| Number of pathogens $\geq$ 2 | 1.45 (0.82–2.58) | 0.2063 | | |
| Use characteristics of polymyxin B | | | | |
| Loading dose (%) | 1.65 (0.94–2.92) | 0.0821 | 1.84 (1.01–3.38) | 0.0491 |
| Cumulative dose, mg | 1.00 (1.00–1.00) | 0.9541 | | |
| Daily dose/actual body weight, mg/kg/d | 1.16 (0.79–1.69) | 0.4539 | | |
| Daily dose/ideal body weight, mg/kg/d | 1.44 (0.92–2.26) | 0.1095 | | |
| Daily dose/actual body weight < 2.5 mg/kg/d (%) Reference group: 2.5–3 mg | 1.24 (0.43–3.61) | 0.6936 | | |
| Daily dose/actual body weight > 3 mg/kg/d (%) Reference group: 2.5–3 mg | 6.07 (1.11–33.24) | 0.0378 | | |
| Daily dose/ideal body weight < 2.5 mg/kg/d (%) Reference group: 2.5–3 mg | 0.75 (0.28–2.00) | 0.569 | | |
| Daily dose/ideal body weight > 3 mg/kg/d (%) Reference group: 2.5–3 mg | 2.94 (0.79–10.98) | 0.109 | | |
| Treatment duration, d | 1.00 (0.98–1.03) | 0.9619 | | |
| Frequency twice a day (%) Reference: QD | 0.61 (0.18–2.06) | 0.4238 | | |
| Frequency three times a day (%) Reference: QD | 0.37 (0.07–1.89) | 0.2318 | | |
| Highest serum creatinine concentration during hospitalization | 1.01 (1.01–1.02) | <.0001 | | |
| Concomitant drugs | | | | |
| Vancomycin | 2.56 (1.45–4.55) | 0.0013 | | |
| Aminoglycosides[d] | >999.9 (<0.001–>999.9) | 0.9876 | | |
| Amphotericin B | 2.20 (1.02–4.76) | 0.0445 | | |
| Acyclovir | — | — | | |
| Vasopressor | 1.78 (1.01–3.11) | 0.0449 | | |
| Methotrexate | — | — | | |
| Cis-platinum | — | — | | |
| Meropenem | 0.90 (0.53–1.52) | 0.6845 | | |
| One nephrotoxic drug | 2.25 (1.06–4.79) | 0.0356 | 2.17 (0.95–4.99) | 0.0674 |
| Receipt of $\geq$2 nephrotoxic drugs | 2.93 (1.38–6.24) | 0.0052 | 3.56 (1.55–8.18) | 0.0029 |

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; $FiO_2$, fractional inspired oxygen; HAP, hospital-acquired pneumonia; HR, hazard ratio; ICU, intensive care unit; $PaO_2$, arterial oxygen partial pressure; QD, once a day; SOFA, sequential organ failure assessment.

[a] Chronic respiratory diseases included emphysema, chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung disease, chronic pulmonary hypertension, and pulmonary fibrosis.

[b] Chronic cardiovascular diseases included hypertension, coronary atherosclerotic heart disease, and congestive heart failure.

[c] Chronic kidney diseases included glomerulonephritis and nephrotic syndrome.

[d] Aminoglycosides included gentamicin, tobramycin, and amikacin.

**Table 3**
Clinical characteristics of patients with different AKI stages

| | AKI 1 stage group (N = 43) | AKI 2 stage group (N = 22) | AKI 3 stage group (N = 19) | P value |
|---|---|---|---|---|
| Demographics | | | | |
| Sex, male | 31 (72.1) | 15 (68.2) | 15 (78.9) | 0.7384 |
| Age, years | 57.95 ± 16.4 | 64.09 ± 17.76 | 66.11 ± 15.2 | 0.1418 |
| Actual body weight, kg | 64.53 ± 12.47 | 66.97 ± 24.43 | 67.17 ± 14.02 | 0.8312 |
| Ideal body weight, kg | 50.23 ± 2.1 | 50.01 ± 2.22 | 50.9 ± 1.69 | 0.4584 |
| Body mass index, kg/m$^2$ | 22.44 ± 4.02 | 23.53 ± 7.3 | 23.28 ± 3.88 | 0.7298 |
| Charlson comorbidity index | 1.49 ± 1.76 | 1.86 ± 2.01 | 2.84 ± 2.48 | 0.0551 |
| Concomitant diseases and background | | | | |
| Chronic respiratory diseases[a] | 21 (48.8) | 9 (40.9) | 10 (52.6) | 0.7384 |
| Chronic cardiovascular diseases[b] | 17 (39.5) | 12 (54.5) | 12 (63.2) | 0.7356 |
| Diabetes | 7 (16.3) | 5 (22.7) | 5 (26.3) | 0.1887 |
| Chronic kidney diseases[c] | 5 (11.6) | 1 (4.5) | 3 (15.8) | 0.6260 |
| Base creatinine, $\mu$ mol/L[e] | 63.40 ± 22.00 | 79.90 ± 40.40 | 88.00 ± 226.00 | 0.0016 |
| Severity at CRE/CRAB HAP diagnosis | | | | |
| SOFA score | 6.07 ± 3.83 | 6.45 ± 2.84 | 6.42 ± 3.2 | 0.8870 |
| APACHE II score | 16.47 ± 6.42 | 17.45 ± 6.69 | 15.95 ± 4.53 | 0.7181 |
| Estimated glomerular filtration rate, mL/min/1.73 m$^2$ | 109.45 ± 27.36 | 83.97 ± 37.39 | 74.32 ± 35.23 | 0.0002 |
| Serum creatinine, $\mu$ mol/L[e] | 65.50 ± 32.40 | 78.00 ± 56.70 | 97.30 ± 52.00 | 0.0022 |
| Bilirubin, $\mu$ mol/L | 28.27 ± 39.96 | 12.77 ± 7.1 | 51.1 ± 98.75 | 0.0899 |
| Albumin, g/L | 35.06 ± 7.18 | 32.69 ± 4.65 | 31.58 ± 6.8 | 0.1335 |
| Procalcitonin, $\mu$g/L[e] | 0.90 ± 1.17 | 0.68 ± 2.34 | 1.25 ± 3.22 | 0.9951 |
| C-reactive protein, mg/L[e] | 43.10 ± 107.75 | 45.70 ± 97.32 | 63.90 ± 80.96 | 0.9744 |
| Neutrophil count, $10^9$/L | 11.02 ± 5.15 | 8.28 ± 5.20 | 14.60 ± 18.20 | 0.1290 |
| Erythrocyte sedimentation rate, mm/h | 37.20 ± 30.50 | 48.89 ± 28.43 | 26.33 ± 28.36 | 0.4653 |
| $PaO_2/FiO_2$ ratio | 212.65 ± 113.24 | 194.8 ± 111.94 | 278.67 ± 115.06 | 0.0732 |
| Mechanical ventilation | 24 (72.7) | 14 (70) | 7 (53.8) | 0.4547 |
| ICU admission | 41 (95.3) | 20 (90.9) | 19 (100) | 0.5421 |
| Sepsis | 9 (20.9) | 6 (27.3) | 4 (21.1) | 0.6774 |
| Sepsis shock | 17 (39.5) | 5 (22.7) | 8 (42.1) | |
| Pathogens at CRE/CRAB HAP diagnosis | | | | |
| Carbapenem-resistant *Klebsiella pneumoniae* | 25 (58.1) | 14 (63.6) | 17 (89.5) | 0.0512 |
| Carbapenem-resistant *Escherichia coli* | 3 (7) | 0 (0) | 0 (0) | 0.4228 |
| Other CRE | 7 (16.3) | 3 (13.6) | 3 (15.8) | 1.0000 |
| CRAB | 28 (65.1) | 14 (63.6) | 15 (78.9) | 0.4968 |
| Carbapenems-resistant *Pseudomonas aeruginosa* | 16 (37.2) | 5 (22.7) | 10 (52.6) | 0.1409 |
| Number of pathogens ≥ 2 | 31 (72.1) | 15 (68.2) | 15 (78.9) | 0.7384 |
| Use characteristics of polymyxin B | | | | |
| Loading dose | 19 (44.2) | 7 (31.8) | 4 (21.1) | 0.1951 |
| Cumulative dose, mg | 1421.05 ± 856.93 | 1600 ± 1321.71 | 1242.11 ± 806.27 | 0.5148 |
| Daily dose/actual body weight, mg/kg/d | 1.92 ± 0.64 | 1.83 ± 0.6 | 2.42 ± 2.33 | 0.3235 |
| Daily dose/ideal body weight, mg/kg/d | 2.37 ± 0.68 | 2.33 ± 0.61 | 2.85 ± 2.39 | 0.3916 |
| Daily dose/actual body weight < 2.5 mg/kg/d | 36 (83.7) | 20 (90.9) | 16 (84.2) | 0.5389 |
| Daily dose/actual body weight > 3 mg/kg/d | 3 (7.0) | 1 (4.5) | 3 (15.8) | |
| Daily dose/ideal body weight < 2.5 mg/kg/d | 32 (74.4) | 17 (77.3) | 16 (84.2) | 0.5846 |
| Daily dose/ideal body weight > 3 mg/kg/d | 7 (16.3) | 2 (9.1) | 3 (15.8) | |
| Frequency twice a day | 41 (95.3) | 19 (86.4) | 15 (78.9) | 0.2366 |
| Frequency three times a day | 1 (2.3) | 1 (4.5) | 2 (10.5) | |
| Treatment duration, d | 13.05 ± 9.86 | 14.77 ± 12.97 | 11.74 ± 10.52 | 0.6682 |
| Highest serum creatinine concentration during hospitalization | 145.77 ± 33.4 | 220.64 ± 31 | 412.72 ± 128.39 | <.0001 |
| Concomitant nephrotoxins | | | | |
| Vancomycin | 20 (46.5) | 8 (36.4) | 6 (31.6) | 0.5398 |
| Aminoglycosides[d] | 0 (0) | 1 (4.5) | 1 (5.3) | 0.2352 |
| Amphotericin B | 8 (18.6) | 4 (18.2) | 3 (15.8) | 1.0000 |
| Acyclovir | 0 (0) | 0 (0) | 0 (0) | |
| Vasopressor | 16 (37.2) | 9 (40.9) | 7 (36.8) | 0.9508 |
| Methotrexate | 0 (0) | 0 (0) | 0 (0) | |
| Cis-platinum | 0 (0) | 0 (0) | 0 (0) | |
| Meropenem | 21 (48.8) | 12 (54.5) | 11 (57.9) | 0.7829 |
| One nephrotoxic drug | 20 (46.5) | 9 (40.9) | 5 (26.3) | 0.4279 |
| Receipt of ≥2 nephrotoxic drugs | 18 (41.9) | 11 (50) | 9 (47.4) | |

Data are presented as mean ± standard deviation or N (%), unless otherwise indicated.
APACHE, acute physiology and chronic health evaluation; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; $FiO_2$, fractional inspired oxygen; HAP, hospital-acquired pneumonia; ICU, intensive care unit; SOFA, sequential organ failure assessment; $PaO_2$, arterial oxygen partial pressure.
[a] Chronic respiratory diseases included emphysema, chronic obstructive pulmonary disease, asthma, bronchiectasis, interstitial lung disease, chronic pulmonary hypertension, and pulmonary fibrosis.
[b] Chronic cardiovascular diseases included hypertension, coronary atherosclerotic heart disease, and congestive heart failure.
[c] Chronic kidney diseases included glomerulonephritis and nephrotic syndrome.
[d] Aminoglycosides included gentamicin, tobramycin, and amikacin.
[e] Data are presented as median ± interquartile range.

affect renal function because this behavior is likely to increase the probability of AKI in patients.

This study did not find that daily dose, cumulative dose, and the duration of polymyxin B to be independent factors related to the occurrence of AKI. Interestingly, multiple studies have shown that polymyxin B has dose-dependent nephrotoxicity. Elias et al. analyzed the predictors of nephrotoxicity in 235 patients (Elias et al. 2010). Patients receiving ≥200 mg of polymyxin B per day had an adjusted OR of 4.5 (1.6–12.9 for the development of severe renal impairment). Nelson et al. evaluated the safety and efficacy of polymyxin B in 109 patients (Nelson et al. 2015). In this analysis, a dose of ≥250 mg per day was associated with a higher incidence of AKI (8/12, 67%), whereas the rate of AKI in patients receiving lower doses was 31/97 ((32%), P = 0.03). In the present study's multivariate analysis, a daily dose of 250 mg or more was an independent predictor of AKI (OR, 4.32; 95% CI, 1.15–16.25). Similarly, Rigatto et al. assessed the risk factors for AKI in patients receiving polymyxin B treatment (Rigatto et al. 2015). The results showed that the proportion of AKI was 33/103 (32%), 109/202 (54%), and 47/105 (44%) among patients who received <150 mg, 150–199 mg, and ≥200 mg per day, respectively, P = 0.001. In the multivariate analysis, a polymyxin B dose ≥ 150 mg per day was highly correlated with the occurrence of AKI (HR, 9.81; 95% CI, 2.37–40.62), whereas a polymyxin B dose ≥ 200 mg per day was not associated with an additional risk. In this study, the homogenization of the dose of polymyxin B among patients might be the main reason for the failure to find a relationship between AKI and the dose of polymyxin B. The drug had been in China for a short time, and its clinical application was not widespread. The dosage used by clinicians was relatively single (the dosage not adjusted according to the weight of the patient), and the phenomenon of homogeneity accounted for a larger proportion. Our data also showed that nearly 90% of patients had a maintenance dose lower than the recommended dose (Tsuji et al. 2019). Despite this, the impact of the loading dose of polymyxin B on AKI still suggests that the dosage of polymyxin B might be a key factor in the occurrence of AKI.

This study did not exclude patients with a history of CKD. Chawla et al. (2014) have suggested that AKI and CKD are not two independent events but are closely interconnected; CKD is a high-risk factor for AKI, and the latter is a high-risk factor for the aggravation of the former (Chawla et al. 2014). Some studies have reported that persistent CKD increases the risk for AKI by as much as 10 times (Xue et al. 2006; Ishani et al. 2009). AKI itself may progress to CKD or exacerbate pre-existing CKD (Ishani et al. 2009; Coca et al. 2012). In addition, after taking into account the risk factors of CKD, such as diabetes and hypertension, AKI was independently associated with the prognosis of CKD, further supporting that the two are correlated (Xue et al. 2006; Wald et al. 2009; Ishani et al. 2009, 2011). Noteworthy, the progression mechanism of renal insufficiency in CKD and AKI may not be similar. Indeed, Baldwin (1977) proposed for the first time that the progression mechanism of CKD may be independent of acute pathological disorder or injury. Moreover, there is evidence that a small increase in serum creatinine concentration is a nonlinear risk factor associated with short-term or long-term adverse outcomes regardless whether the patient has CKD or not (Chertow et al. 2005; Coca et al. 2007). In this study, we did not find that previous CKD was an independent risk factor for the occurrence of AKI. One possible explanation is the small number of patients included in this study.

This study has several limitations. The first limitation occurs during patient screening. Multidrug-resistant pathogens are often secondary to nosocomial infections, and many times, this event occurs in the middle and late stages of the disease. Severe conditions often increase the risk for AKI, which may occur before medication. It is not enough to simply exclude patients with AKI at the time of admission, as they may develop AKI after admission due to other factors (such as serious illness or drug factors). Before evaluating the relationship between polymyxin B and AKI, the ideal state was to exclude patients with AKI before medication. However, due to the limitations of retrospective studies and the complexity of the actual clinical situation (many patients do not specifically test renal function before medication), it is impossible to accurately exclude patients who are determined to have no AKI before medication. However, we excluded patients who had AKI at the time of diagnosis of HAP to analyze the relationship between polymyxin B and AKI more accurately. We believe that this time point is the closest to the use of polymyxin B. Second, it was difficult for us to choose other drugs for comparison. Clinicians often choose a variety of antibiotics for the infection of carbapenem-resistant pathogens, such as carbapenems or tigecycline, which greatly increases the difficulty of choosing a control group. In addition, since this is a multicenter clinical study, there may be differences in the infusion time, nursing methods, and patient groups of each hospital. Finally, the study did not follow up on the long-term prognosis of patients with AKI, so the effect of AKI on the long-term cardiac and renal function of patients could not be analyzed. Some studies have shown that AKI may cause CKD regardless of the cause of AKI (Pogue and Tam, 2019).

## Conclusions

The use of polymyxin B loading doses and the combined use of multiple nephrotoxic drugs are independent risk factors for polymyxin B-related AKI. The severity of AKI may be higher in patients with elevated baseline creatinine levels. A well-designed prospective study is needed for further research.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Funding

This work was supported by CAMS Innovation Fund for Medical Sciences (Grant No. 2018-I2M-1-003). The funder had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

## Ethical Approval statement

The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital (No. 2018-146-K103). The other hospitals accepted the approval by the Ethics Committee of the China-Japan Friendship Hospital.

## Acknowledgments

We thank all the researchers from all participating hospitals who participated in the collection of patient information, including Tiantian Zhao from The First Affiliated Hospital of Nanchang University, Yingxiao Wu from Fujian Medical University Union Hospital, Yifei Chen from Zhongnan Hospital of Wuhan University, Weining Xiong from Tongji Hospital, Xinliang He from Union Hospital, Jianrong Zhu from Wuxi People's Hospital, Mingyue Wang from The First Affiliated Hospital of Nanjing Medical University, Min Yang from The Second Xiangya Hospital, Donghui Zhang from Zhongshan Hospital, Xin Xu from The Second Affiliated Hospital of

Zhejiang University School of Medicine, Jinyu Pan from Zhejiang Provincial People's Hospital, and Qian Sang from the First Affiliated Hospital of Zhengzhou University. We would also like to thank Editage (www.editage.cn) for English language editing.

## References


Akajagbor DS, Wilson SL, Shere-Wolfe KD, Dakum P, Charurat ME, Gilliam BL. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis 2013;57(9):1300–3.

Azad MAK, Finnin BA, Poudyal A, Davis K, Li J, Hill PA, Nation RL, Velkov T, Li J. Polymyxin B induces apoptosis in kidney proximal tubular cells. Antimicrob Agents Chemother 2013;57(9):4329–35.

Azad MA, Roberts KD, Yu HH, Liu B, Schofield AV, James SA, et al. Significant accumulation of polymyxin in single renal tubular cells: a medicinal chemistry and triple correlative microscopy approach. Anal Chem 2015a;87(3):1590–5.

Azad MA, Akter J, Rogers KL, Nation RL, Velkov T, Li J. Major pathways of polymyxin-induced apoptosis in rat kidney proximal tubular cells. Antimicrob Agents Chemother 2015b;59(4):2136–43.

Baldwin DS. Poststreptococcal glomerulonephritis. A progressive disease? Am J Med 1977;62(1):1–11.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.

Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371(1):58–66.

Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16(11):3365–70.

Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis 2007;50(5):712–20.

Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81(5):442–8.

Elias LS, Konzen D, Krebs JM, Zavascki AP. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. J Antimicrob Chemother 2010;65(10):2231–7.

Esaian D, Dubrovskaya Y, Phillips M, Papadopoulos J. Effectiveness and tolerability of a polymyxin B dosing protocol. Ann Pharmacother 2012;46(3):455–6.

Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care 2006;10(1):R27.

Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, Slinin Y, Ensrud KE. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med 2011;171(3):226–33.

Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009;20(1):223–8.

Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29.

Kubin CJ, Ellman TM, Phadke V, Haynes LJ, Calfee DP, Yin MT. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. J Infect 2012;65(1):80–7.

Kvitko CH, Rigatto MH, Moro AL, Zavascki AP. Polymyxin B versus other antimicrobials for the treatment of pseudomonas aeruginosa bacteraemia. J Antimicrob Chemother 2011;66(1):175–9.

Lee YJ, Wi YM, Kwon YJ, Kim SR, Chang SH, Cho S. Association between colistin dose and development of nephrotoxicity. Crit Care Med 2015;43(6):1187–93.

Mendes CA, Cordeiro JA, Burdmann EA. Prevalence and risk factors for acute kidney injury associated with parenteral polymyxin B use. Ann Pharmacother 2009;43(12):1948–55.

Modi AR, Kovacs CS. Hospital-acquired and ventilator-associated pneumonia: diagnosis, management, and prevention. Cleve Clin J Med 2020;87(10):633–9.

Nelson BC, Eiras DP, Gomez-Simmonds A, Loo AS, Satlin MJ, Jenkins SG, Whittier S, Calfee DP, Furuya EY, Kubin CJ. Clinical outcomes associated with polymyxin B dose in patients with bloodstream infections due to carbapenem-resistant Gram-negative rods. Antimicrob Agents Chemother 2015;59(11):7000–6.

Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. Diagn Microbiol Infect Dis 2009;65(4):431–4.

Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant gram-negative bacteria. Antimicrob Agents Chemother 2003;47(8):2659–62.

Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, Lev S, Leon P, Raskin M, Yahav D, Leibovici L. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother 2010;65(5):1019–27.

Phe K, Lee Y, McDaneld PM, Prasad N, Yin T, Figueroa DA, Musick WL, Cottreau JM, Hu M, In Tam VH. vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother. 2014;58(5):2740–6.

Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, Lephart P, Kaye KS. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis 2011;53(9):879–84.

Pogue JM, Tam VH. Toxicity in patients. Adv Exp Med Biol 2019;1145:289–304.

Ramasubban S, Majumdar A, Das PS. Safety and efficacy of polymyxin B in multidrug resistant Gram-negative severe sepsis and septic shock. Indian J Crit Care Med 2008;12(4):153–7.

Rigatto MH, Behle TF, Falci DR, Freitas T, Lopes NT, Nunes M, Costa LW, Zavascki AP. Risk factors for acute kidney injury (AKI) in patients treated with polymyxin B and influence of AKI on mortality: a multicentre prospective cohort study. J Antimicrob Chemother 2015;70(5):1552–7.

Rigatto MH, Oliveira MS, Lauro P-N, MT, Tanitap V, Levin AS, Carrilho CM, Tuon FF, Cardoso DE, Lopes NT, Falci DR, Zavascki AP. Multicenter Prospective Cohort Study of Renal Failure in Patients Treated with colistin versus polymyxin B. Antimicrob Agents Chemother 2016;60(4):2443–9.

Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, Behle TF, Saitovitch D, Wang J, Forrest A, Nation RL, Zavascki AP, Li J. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis. J Antimicrob Chemother 2013;68(3):674–7.

Sobieszczyk ME, Furuya EY, Hay CM, Pancholi P, Della-Latta P, Hammer SM, Kubin CJ. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. J Antimicrob Chemother 2004;54(2):566–9.

Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, Sethi S, Lee EJ. GFR estimating equations in a multiethnic Asian population. Am J Kidney Dis 2011;58(1):56–63.

Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, Giacobbe DR, Viscoli C, Giamarellou H, Karaiskos I, Kaye D, Mouton JW, Tam VH, Thamlikitkul V, Wunderink RG, Li J, Nation RL, Kaye KS. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39(1):10–39.

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LGThe SOFA. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–10.

Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JGUniversity of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009;302(11):1179–85.

Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, Himmelfarb J, Collins AJ. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 2006;17(4):1135–42.

Zhou J, Liu Y, Tang Y, Liu F, Zhang L, Zeng X, Feng Y, Tao Y, Yang L, Fu P. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. Int Urol Nephrol 2016;48(1):125–32.