Risk Factors for Polymyxin B-associated Acute Kidney Injury in Patients with Severe Gram-Negative Bacterial Infections

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Research

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Abstract

Background

The occurrence of polymyxin B-associated kidney injury (AKI) has been reported in recent years. The purpose of this study was to investigate the risk factors for polymyxin B-associated AKI and renal function recovery in patients with severe gram-negative bacterial infections.

Methods

We conducted a retrospective review of all severe gram-negative bacterial infection patients treated with polymyxin B admitted to Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing City, China, between December 2018 and May 2021. Based on the new onset of AKI within 1 week after polymyxin B treatment, patients were divided into two groups: the AKI group and the non-AKI group. Among the AKI group, the patients were divided into an AKI recovery group and a nonrecovery AKI group according to the recovery of renal function within one week of polymyxin B discontinuation. Clinical manifestations, laboratory findings, treatments and outcomes in these patients were collected and analysed.

Results

A total of 188 cases were included. There were 87 cases in the AKI group (46.3%) and 101 cases in the non-AKI group (53.7%). Compared with the non-AKI group, the proportions of hypertension, shock and bacteremia were significantly higher in the AKI group ($P < 0.05$). In the AKI group, the platelet count was significantly decreased ($P < 0.05$), while the serum creatinine (Scr) of the AKI group was dramatically higher than that of the non-AKI group ($P< 0.001$). Compared with the non-AKI group, the loading dose and daily dose of polymyxin B in the AKI group were obviously higher ($P< 0.05$). The proportion of polymyxin + carbapenems in the AKI group was significantly elevated compared with that in the non-AKI group ($P<0.05$). The 28-d mortality in the AKI group was significantly higher than that in the non-AKI group ($P<0.05$). Multivariate logistic regression analysis indicated that cardiopulmonary resuscitation (CPR) history and baseline Scr ≥60 μmol/L before polymyxin B administration were independent risk factors for AKI ($P<0.05$). Fifty-nine patients met the criteria for AKI recovery analysis from the AKI group. There were 27 cases of unrecovered AKI (45.8%) and 32 cases of recovered AKI (54.2%). Multivariate logistic regression analysis identified male sex as an independent predictor for unrecovered AKI in patients with polymyxin B treatment.

Conclusions

Polymyxin B-associated AKI occurs frequently in patients with severe gram-negative bacterial infection, and some patients cannot recover within one week after discontinuation of polymyxin B. Scr≥60 μmol/L before medication was found to be the only independent risk factor for polymyxin B-associated AKI, and it was more difficult for male patients to recover from AKI.

Background

As early as the 1950s, polymyxin B, a peptide antibiotic, was used in the clinic but was replaced by other antibiotics due to its narrow antibacterial spectrum and strong nephrotoxicity. However, due to the emergence of drug-resistant bacteria in recent years, the use of polymyxin B has started again. Compared with polymyxin E, polymyxin B has relatively low nephrotoxicity and has been recommended by IDSA as a salvage treatment for multidrug-resistant gram-negative bacteria[1, 2].

Polymyxin B is mainly eliminated by nonrenal pathways, and some clinical pharmacokinetic (PK) studies have shown that its drug clearance ability is not related to renal function[3, 4]. Therefore, it is generally accepted that the incidence of drug-related acute kidney injury (AKI) caused by polymyxin B is limited. The latest International Consensus Guidelines for the Optimal Use of the Polymyxins in 2019 do not recommend dose adjustment according to the creatinine clearance rate, and patients with renal insufficiency do not need to adjust the dose[2]. However, the occurrence of polymyxin B-associated AKI has been reported in recent years, and the incidence of polymyxin B-associated AKI has been reported to range from 12.7–60%[5–7]. On one hand, the incidence of polymyxin B-associated AKI is influenced by risk factors related to the underlying disease, severity of the disease, age, concurrent nephrotoxic medication, hypoalbuminemia, and drug dose. On the other hand, the diagnostic criteria for AKI are different in different studies, leading to significant differences in reported AKI incidence[6, 8, 9].

Therefore, this study aims to investigate the incidence and risk factors for polymyxin B-associated AKI and the risk factors for unrecovered AKI and to provide a theoretical basis for optimizing the treatment strategy of polymyxin B in patients with severe gram-negative bacterial infections.

Methods

Study population

We conducted a retrospective review of critically ill patients treated with polymyxin B admitted to Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing, China, between December 2018 and May 2021. The inclusion criteria were age 18–90 years, duration of polymyxin B ≥ 72 hours and hospitalization stay ≥ 72 hours. Exclusion criteria were age < 18 years or > 90 years; existing renal insufficiency (acute or chronic); duration of polymyxin B treatment of less than 72 hours; patients with blood purification treatment during polymyxin B treatment; survival time or hospitalized stay < 72 h.

Patients were divided into two groups based on the onset of new AKI within 1 week after treatment with polymyxin B: □ AKI group and □ non-AKI group. According to KDIGO's AKI diagnostic criteria published in 2012[10], AKI can be diagnosed if one of the following conditions is met: (1) serum creatinine elevation ≥ 26.5 μmol/L within 48 hours; or (2) serum creatinine increased by more than 1.5 times the baseline value within 7 days.

Among the AKI group, the patients were divided into the AKI recovered group and the unrecovered AKI group according to the recovery of renal function within one week of polymyxin B discontinuation: (1) recovered AKI group, defined as Scr ≤ 125% baseline value within one week; (2) unrecovered AKI group, defined as Scr > 125% baseline value within one week[11].

Data Collection

Investigators collected clinical data from the electronic medical records system of Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing, China. between December 2018 and May 2021. Demographic data, underlying diseases, complications, laboratory findings, comorbidities, loading dose, daily dose, duration and combination of polymyxin B treatments, renal function before treatment, one week after polymyxin B administration, and one week after discontinuation, and overall prognosis were collected.

Statistical analysis

All statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, USA). Data are reported as percentages for categorical variables and as the means ± standard deviations (SD) or medians with interquartile ranges (IQRs), as appropriate, for continuous variables. Chi-square tests or Fisher's exact tests were used for categorical variables. The t-test or Mann–Whitney U test was used for continuous variables, as appropriate. All tests of significance were 2-sided, and $p < 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to determine the risk factors for the development of AKI and recovery from AKI. The results are reported as adjusted odds ratios for mortality with the corresponding 95% confidence intervals.

Results

Clinical characteristics

Between December 2018 and May 2021, a total of 212 patients with polymyxin B treatment for ≥ 72 h were recorded in the electronic medical records system of Nanjing Drum Tower Hospital. Twenty patients who had existing AKI or CKD and four patients without serum creatinine measurements before or one week after polymyxin B treatment were excluded. Of the 188 patients who met the inclusion criteria for AKI analysis, 87 (46%) cases were included in the AKI group, and 101 (54%) were included in the non-AKI group. According to the serum creatinine level one week after the discontinuation of polymyxin B, 7 patients who showed no serum creatinine results one week after the discontinuation of polymyxin B and 21 patients who were discharged or died within 7 days after the discontinuation of polymyxin B were excluded. Finally, 59 cases were included in the AKI recovery analysis, of which 27 cases were in the unrecovered AKI group and 32 cases were in the recovered group.

Table 1 presents the differences in baseline characteristics, comorbidities, laboratory findings before polymyxin B treatment and outcome parameters between the AKI and non-AKI groups. Compared with the

non-AKI group, the proportion of males in the AKI group was higher (78.2%, $P < 0.05$). The proportion of shock, bacteremia and cardiopulmonary resuscitation (CPR) history in the AKI group was obviously higher than that in the non-AKI group ($P < 0.05$). The platelet count in the AKI group was dramatically lower than that in the non-AKI group ($P < 0.05$), while the procalcitonin (PCT) and C-reactive protein (CRP) levels in the AKI group were higher than those in the non-AKI group ($P < 0.05$). The Scr of the AKI group before polymyxin B treatment was obviously higher than that of the non-AKI group ($P < 0.001$). The 28-d mortality in the AKI group was 28.5%, which was higher than that in the non-AKI group (15.8%, $P < 0.05$).

Table 1
Clinical data of the AKI and non-AKI groups

	AKI group (n = 87)	**Non-AKI group (n = 101)**	***p value***
Demographics			
Age (years)	63.48 ± 16.08	64.17 ± 16.74	0.776
Gender (male),n(%)	68(78.2)	65(64.4)	0.027
Comorbidities (n,%)			
Hypertension	45(51.7)	41(40.6)	0.084
Diabetes	20(23)	24(23.8)	0.520
Respiratory failure	52(59.8)	60(59.5)	0.539
Shock	47(54)	27(28.7)	< 0.001
Bacteremia	43(49.4)	24(23.8)	< 0.001
Malignant disease	9(10.3)	18(17.8)	0.105
Immune system diseases	17(19.5)	20(19.8)	0.556
CPR history	8(9.2)	1(1)	0.01
Laboratory findings (before polymyxin B treatment) (n, median,IQR)			
WBC (*10^9/L)	11(8–15.8)	10(6.95–14)	0.251
Platelets (*10^9/L)	154(80–232)	194(117–269)	0.04
PCT (mg/L)	0.708(0.196–2)	0.257(0.046–1)	0.007
CRP (mg/L)	94(54.73–133.2)	50.1(20.2–100)	< 0.001
ALT (U/L)	23.65(15.03–46.25)	23(13.2–44.35)	0.897
AST (U/L)	29.05(19.83–52.98)	28(19.93–49.75)	0.885
TB (umol/L)	12.75(7.93–27.73)	11.7(6.6–22.05)	0.087
BUN (mmol/L)	10.65(7.6–16.49)	9.28(6.09–14.40)	0.123
Scr (umol/L)	68(53–94.75)	41(34–58)	< 0.001
Outcomes			

AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; WBC; white blood cell; PCT, procalcitonin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; TB, total bilirubin; BUN, blood urea nitrogen; Scr; serum creatinine; LOS, length of stay

	AKI group (n = 87)	Non-AKI group (n = 101)	*p value*
LOS	35.73 ± 21.39	37.76 ± 25.55	0.573
28-d mortality,n(%)	25(28.7)	16(15.8)	0.025

AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; WBC; white blood cell; PCT, procalcitonin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; TB, total bilirubin; BUN, blood urea nitrogen; Scr; serum creatinine; LOS, length of stay

The administration of polymyxin B in the AKI and non-AKI groups is shown in Table 2. The total dosage of polymyxin B in the two groups was not significantly different, but the daily dose and loading dose in the AKI group were dramatically higher than those in the non-AKI group ($P < 0.05$), and there was no difference in the polymyxin B duration between the two groups. The proportion of concomitant carbapenems in the AKI group was 65.5%, which was obviously higher than that in the AKI group ($P < 0.05$).

Table 2
Comparison of treatment with polymyxin B in AKI and non-AKI groups

	AKI group (n = 87)	Non-AKI group (n = 101)	*p value*
Total dosage(mg)	1566.44 ± 987.58	1538.60 ± 987.58	0.794
Daily dosage(mg/d)	138.51 ± 30.21	123.76 ± 32.86	0.002
Loading dosage(mg)	137.36 ± 28.75	121.29 ± 28.59	< 0.001
Duration(days)	10.98 ± 5.83	11.21 ± 6.23	0.699
Polymyxin B monotherapy, n(%)	11(12.6)	17(16.8)	0.276
Concomitant with β-lactam, n(%)	7(8)	15(14.9)	0.111
Concomitant with carbapenem, n(%)	57(65.5)	35(34.7)	< 0.001
Concomitant with tigecycline, n(%)	26(29.9)	43(42.6)	0.049
Concomitant with tigecycline and carbapenem,n(%)	3(3.4)	4(4)	0.561

Univariate and multivariate analyses of risk factors for the development of AKI in patients with polymyxin B treatment

Univariate logistic regression showed that shock, bacteremia, CPR history, platelets < $150*10^9$/L, PCT ≥ 0.5 mg/L, CRP ≥ 100 mg/L, Scr ≥ 60 μmol/L, daily dose of polymyxin B ≥ 150 mg, loading dose of polymyxin B ≥ 150 mg, and polymyxin B concomitant with carbapenem were risk factors for the development of AKI. Multivariate logistic regression analysis identified CPR history and baseline Scr ≥ 60 μmol/L as independent predictors of AKI development for patients with polymyxin B treatment (Table 3).

Table 3
Univariate and multivariate analyses of risk factors for the development of AKI

Variable	Univariate		Multivariate	
	OR (95% CI)	*p value*	OR (95% CI)	*p value*
Shock	2.917(1.596–5.331)	0.001		
Bacteremia	3.135(1.684–5.839)	< 0.001		
CPR history	10.127(1.240–82.669)	0.031	11.217(1.085–115.991)	0.043
Platelets < $150*10^9$/L	1.839(1.020–3.315)	0.043		
PCT ≥ 0.5 mg/L	2.350(1.239–4.458)	0.009		
CRP ≥ 100 mg/L	2.730(1.465–5.089)	0.002		
Scr ≥ 60umol/L	5.796(3.073–10.930)	< 0.001	3.783 (1.557–9.191)	0.003
Daily dose of polymyxin B ≥ 150 mg/d	3.350(1.834–6.118)	< 0.001		
Loading dose of polymyxin B ≥ 150 mg	3.350(1.834–6.118)	0.0001		
polymyxin B Concomitant with carbapenem	3.583(1.961–6.547)	< 0.001		

AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; PCT, procalcitonin; CRP, C-reactive protein

Univariate and multivariate analyses of risk factors for unrecovered AKI in patients receiving polymyxin B treatment

Univariate logistic regression showed that male sex, age ≥ 65 years, shock, diabetes, bacteremia and shock were risk factors for unrecovered AKI in patients with polymyxin B treatment. Multivariate logistic regression analysis identified male sex as the only independent predictor of unrecovered AKI for patients with polymyxin B treatment (Table 4).

Table 4
Univariate and multivariate analyses of risk factors for unrecovered AKI

	Univariate		**Multivariate**	
	OR (95% CI)	*p value*	OR (95% CI)	*p value*
Sex (male)	8.553(1.720–42.521)	0.009	8.062(1.482–43.845)	0.016
Age ≥ 65years	3.333(1.139–9.752)	0.028		
Diabetes	2.865(1.153–7.116)	0.023		
Bacteremia	3.245(1.115–9.450)	0.031		
Shock	3.333(1.139–9.752)	0.028		

Discussion

This retrospective study showed that the incidence of polymyxin B-associated AKI was 46% (87/188) in patients with severe gram-negative bacterial infections admitted to our hospital from December 2018 to May 2021. In other studies, 12.7–60% of polymyxin B-associated AKI was reported due to different patients and different AKI definitions [5–7].

Although the clearance of polymyxin B is mainly through nonrenal excretion, up to 90–95% of the glomerular filtration of polymyxin B is reabsorbed by tubular cells[3, 12]. Several studies have shown a significant accumulation of polymyxin B in the kidneys[13–16]. In an animal study of mice, the distribution of polymyxin B in renal tissue was assessed after intravenous administration with polymyxin-specific monoclonal antibody immunostaining[17], which showed that polymyxin B was concentrated in the renal cortex, especially in proximal tubular cells. Mohammad et al. also reported that the polymyxin concentration in human renal tubule cells was 4760 times higher than the extracellular concentration, indicating that there was an abnormal aggregation of polymyxin in these cells[13]. Therefore, exposure of renal tubule cells to such high concentrations of polymyxin can directly cause damage due to the reabsorption process and intracellular accumulation of polymyxin[3, 18]. These processes may explain why polymyxin B is mainly cleared by nonrenal pathways but also causes renal impairment.

Polymyxin B-associated AKI may be dose-related. In this study, we found that both a loading dose ≥ 150 mg and a daily dose ≥ 150 mg of polymyxin B were risk factors for AKI incidence, but they were not independent risk factors. Another multicentre study of 406 patients also found that a daily dose of polymyxin B ≥ 150 mg was an independent risk factor for AKI[19].

Polymyxin B-associated AKI may be related to the pharmacokinetics (PK) of the drug, but to date, there are very limited clinical data on the PK of polymyxin B[3, 20–22]. Although the polymyxin B specification recommends administering a loading dose and maintenance dose based on patients' weight, studies have found that patients' weight does not affect the drug clearance nor change in vivo PK parameters; thus, the recommended dosage based on patient weight may not be the best way to optimize the dosage of polymyxin B [20]. Peile Wang et al. administered polymyxin B to patients with different renal functions and analysed the PK parameters, which showed that the area under the 24-hour curve (AUCss, 24 h) of polymyxin B in the AKI group was significantly higher than that in the non-AKI group and that AUCss, 24 h > 100 mg/ml.min was an independent risk factor for nephrotoxicity[23].

Polymyxin B-associated AKI may be related to basal renal function. Several studies have shown that renal insufficiency before polymyxin B treatment may be a risk factor for nephrotoxicity[8, 24]. Hamlikitkul et al. used therapeutic doses of polymyxin B in patients with normal renal function and renal insufficiency and found that renal clearance of polymyxin B was significantly lower in patients with renal insufficiency than in patients with normal renal function (2.5 L/h vs. 2.0 L/h)[4]. Other studies have also found that when polymyxin B is administered to patients with different renal functions, creatinine clearance (CrCL) is a key factor affecting PK in polymyxin B. The results of this study showed that the basal Scr before treatment in AKI group was significantly higher than that in non-AKI group and that the basal Scr ≥ 60umol/L was the only independent risk factor for AKI caused by polymyxin B. Although the patient's Scr was still within the normal range of 60–100umol/L at this time, the patient's renal reserve function may have been damaged. Therefore, it is more reasonable to recommend the use of CrCL to guide the dose of polymyxin B.

Polymyxin B-associated AKI may be related to drug combinations. Polymyxin B is recommended in combination (β-amides, carbapenems, avibatan, amtronam) due to high heterogeneity in IDSA guidelines[1]. Studies have shown that polymyxin B combined with tigecycline is an independent risk factor for AKI[25]. In this study, polymyxin B combined with carbapenems was found to be a risk factor for AKI but not an independent risk factor.

In this study, we found that the recovery rate of polymyxin B-associated AKI was 54% (32/59), while in other literature, it was only 33% and 39%[26, 27]. Interestingly, multivariate regression analysis in our study found that male sex was the only independent risk factor for unrecovered polymyxin B-associated AKI and that there was no significant association with the doses and duration of polymyxin B. It has been reported that the combination of polymyxin B and selective oestrogen receptor modulators (SERMs) can enhance the antibacterial activity of polymyxin B against XDR-negative bacteria, which may be a plausible explanation for why male sex was an independent risk factor for unrecovered polymyxin B-associated AKI[28].

This study also has some limitations. First, the study was a retrospective study with sample error. Second, this study failed to collect indicators of long-term renal function recovery after the discontinuation of polymyxin B and could not assess the recovery of polymyxin B-associated AKI. Finally,

the study failed to monitor the concentration of polymyxin B and to investigate the relationships among dose, PK and renal function.

Conclusions

Therefore, the high incidence of polymyxin B-associated AKI should not be ignored. In a significant proportion of patients, renal function does not recover after discontinuation of polymyxin B. Renal function changes should be closely monitored before and after the administration of polymyxin B, and it is recommended to monitor the plasma concentration of polymyxin B in patients with basic renal insufficiency.

Abbreviations

AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; WBC; white blood cell; PCT, procalcitonin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; TB, total bilirubin; BUN, blood urea nitrogen; Scr; serum creatinine; LOS, length of stay

Declarations

Ethical Approval and Consent to participate

This study was approved by the Ethics Committee of Drum Tower Hospital affiliated with the Medical School of Nanjing University. The need to obtain informed consent from individual patients was waived given the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author (Qin Gu) on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding source

Not available.

Authors' contributions

YX and QG made substantial contributions to the conception and design of the study. YX, PL, YL and YJQ acquired the data. NL, QG and JT performed the analysis and interpretation of the data. YX and PL wrote the draft of the article and revised it critically for intellectual content. The final version was approved by all authors. No conflicts of interest exist regarding the submission of this manuscript. The authors declare that the work described is original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part.

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Figures

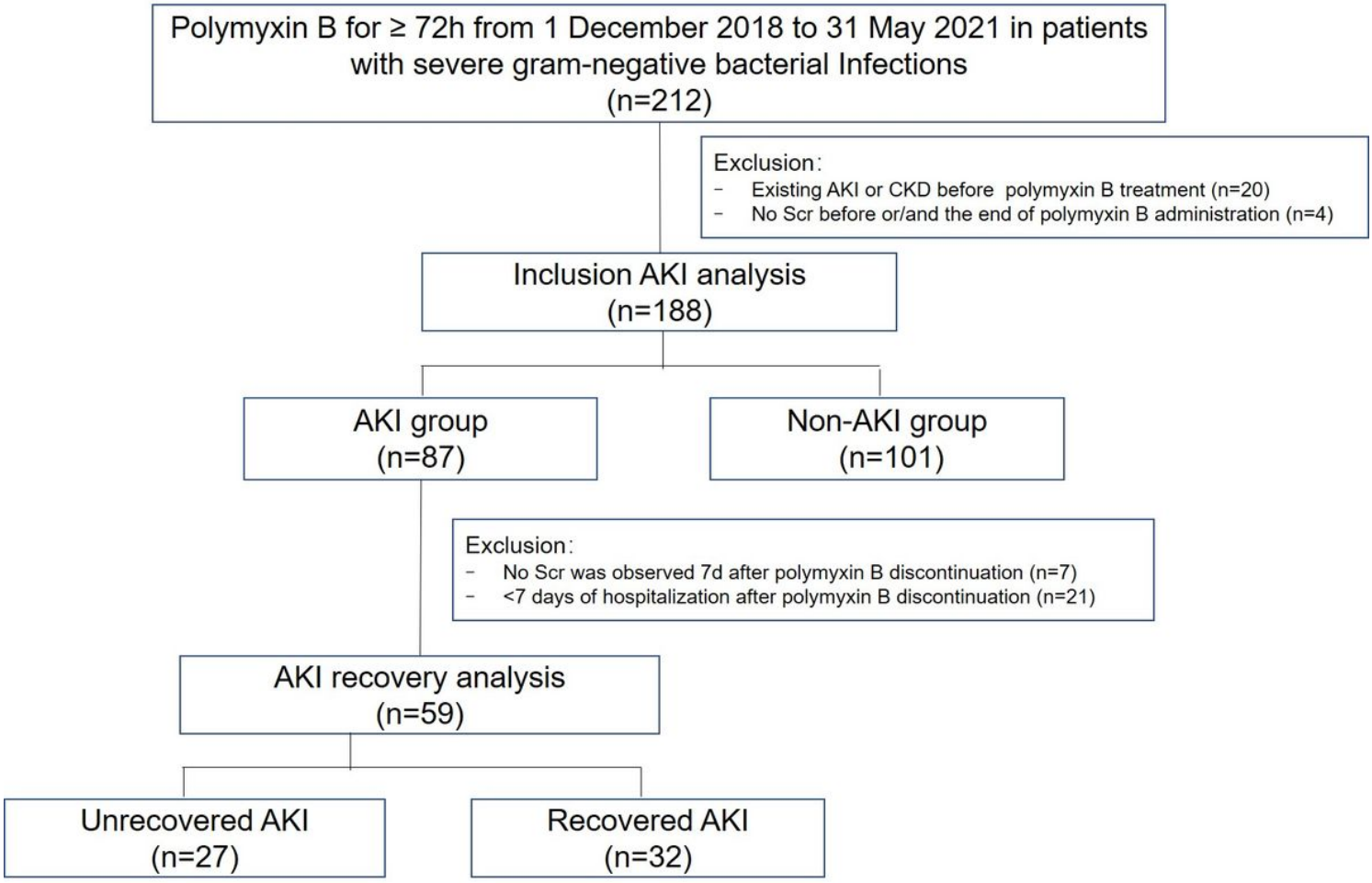

Figure 1

Flow chart of study inclusion process. AKI, acute kidney injury; CKD, chronic kidney disease; Scr, serum creatinine