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ORIGINAL RESEARCH

Risk Factors and Outcomes for Isolation with Polymyxin B-Resistant Enterobacterales from 2018–2022: A Case-Control Study

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Purpose: To analyze the risk factors and clinical outcomes of patients isolated with polymyxin B-resistant (PR) *Enterobacterales* from various clinical specimens to prevent and control the spread of these strains.

Methods: This retrospective case-control study included 72 PR *Enterobacterales*-positive cases and 144 polymyxin B-susceptible (PS) *Enterobacterales* controls from 2018 to 2022. Patients with PR *Enterobacterales* isolated in various clinical cultures were defined as cases. Patients with PS *Enterobacterales* cultures at similar anatomic sites during the same period were randomly selected as controls. Data were collected from clinical and laboratory test records. Bivariable logistic regression and Pearson's chi-square tests were used to assess risk factors.

Results: PR strains were predominantly *Klebsiella pneumoniae* (72.2%) and *Salmonella enteritidis* (8.3%). Of the patients, 66.04% were admitted to an intensive care unit (ICU). Risk factors for isolation with PR strains included chronic heart disease (P = 0.012; odds ratio [OR] 1.15; 95% confidence interval [CI] 1.03–1.28), immunosuppressant use (P = 0.016; OR 1.04 [1.0–1.07), drainage tube [head] (P = 0.006; OR 1.1 [1.0–1.1]), and polymyxin B exposure (P = 0.007; OR 1.03 [1.0–1.06]. With respect to outcomes, admission to an ICU (P = 0.003; OR 7.1 [1.9–25.4]), hypertension (P = 0.035; OR 1.4 [1.02–1.83]), and drainage tube [head] (P = 0.044; OR 1.1 [1.0–1.15]) were associated with treatment failure. Additionally, treatment failure was more frequent in patients (45.83%) than in controls (14.58%).

Conclusion: The major risk factors for isolation with PR strains were chronic heart disease, exposure to immunosuppressants, use of drainage tubes, and polymyxin B exposure. The isolation of PR strains in patients was a predictor of unfavorable outcomes. These findings provide a basis for monitoring the spread of PR *Enterobacterales*.

Keywords: polymyxin B resistance, treatment failure, *Klebsiella pneumoniae*, *Salmonella enteritidis*

Introduction

Multidrug-resistant Gram-negative bacilli have increased worldwide and pose a significant and growing threat that limits the effectiveness of therapeutic regimens.[1] Conventional drugs, such as polymyxin E (colistin) and polymyxin B, are being reconsidered as the last line of defense against multidrug-resistant Gram-negative bacilli infections.[2] Owing to the increased use of colistin in clinical settings, resistance to this antibiotic has increased, particularly among *Klebsiella pneumoniae* isolates, which should be monitored.[3–5] Polymyxin B-resistant (PR) bacterial infections have been reported in both nosocomial and community settings.[6]

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The mechanisms underlying polymyxin B resistance in Gram-negative bacilli mainly involve intrinsic mechanisms, mutations, or adaptation. The selective pressure applied by the polymyxin dose regulates the dynamics of genetic variants within the population. To this end, the super minimum inhibitory concentration (super-MIC) levels (> 4 x MIC) of polymyxin B were reported to have caused the development of irreversible resistance in *Acinetobacter baumannii*.[7] It has been suggested that the principal resistance to this antibiotic in *Enterobacterales* is associated with lipopolysaccharide modification, which is mediated by charged 4-amino-4-deoxy-L-arabinose (L-Ara4N; mediated by *arnBCADTEF*) and/or phosphoethanolamine (pEtN; mediated by *pmrC*, or mobile colistin resistance gene).[8–10] The mobile colistin resistance gene (*mcr-1)* and its variants, *mcr-2* to *mcr-10*, mediate polymyxin B resistance.[6,11–13] A recent study showed that New Delhi metallo-β-lactamase (NDM)-producing MDR *K. pneumoniae* can rapidly attain high-level polymyxin resistance through cellular metabolism plasticity, lipid A modification, and outer membrane remodeling.[14]

In addition to monitoring the rate of resistance to polymyxins and underlying mechanisms, the identification of relevant risk factors in patients with colistin-resistant bacteria is important to prevent the spread of nosocomial infection outbreaks. Several studies have identified risk factors related to patients with colistin-resistant and/or carbapenem-resistant *Enterobacterales* infection or colonization.[4,15–17] However, studies focused on risk factors in Henan Province, China, are limited.

The relevant risk factors and outcomes of patients carrying PR *Enterobacterales* were retrospectively analyzed to provide a reference for the prevention and control of PR *Enterobacterales* infection outbreaks in hospital.

Materials and Methods

Study Participants

This case-control study was performed at a tertiary care teaching hospital with 5000 beds in Henan Province, China, between January 2018 and December 2022. The risk factors related to the isolation of PR *Enterobacterales* were investigated. The case group (n = 72) included patients with PR *Enterobacterales* isolated from various clinical specimens during the study period. Patients with polymyxin B-susceptible (PS) *Enterobacterales* isolated from clinical cultures were controls. The ratio of control to case samples was 2:1. Controls were matched for hospital ward, date of hospitalization, and pathogen with the case in a random manner. The exclusion criteria (n = 23) were as follows: patients with PR *Enterobacterales* isolation from intestinal screening samples during the study period and inadequate clinical or laboratory data, such as transfer or discharge without relevant clinical diagnoses and treatment processes, resulting in unclear patient outcomes. Patients with clinical cultures of *Enterobacterales* (eg, *Providencia* spp., *Proteus* spp., *Morganella morganii*, and *Serratia* spp.) intrinsically resistant to polymyxins were also excluded.

Definition of Outcomes

The outcomes of patients in this study were defined as follows: Treatment failure included patients who died for any reason or were discharged without improvement after the isolation of polymyxin B-resistant strains.

Clinical Data

Data were obtained from electronic medical records. Potential risk factors included demographic properties (age and sex), medical history (hospitalization, transfers between hospitals and departments, intensive care unit [ICU] admission, and surgery), comorbidities, inpatient time, admission diagnosis, antibiotic use, use of invasive medical devices (urinary catheter, mechanical ventilation, drainage tube, and nasogastric tube), and use of immunosuppressive drugs. Diagnosis was classified using the International Classification of Diseases-11 (ICD-11) based on the patient's admission diagnosis.[18]

Microbiological Methods

Bacterial species identification and antimicrobial susceptibility testing were performed using the Phoenix100 automated system according to the manufacturer's recommendations (Becton Dickinson Co., Sparks, MD, USA). The identification of *Salmonella* spp. was based on a serum agglutination test. The polymyxin B MICs of the isolates were determined by

broth microdilution. The results were interpreted using the clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing.[19] Isolates with an MIC higher than 2 mg/L for polymyxin B were considered PR. *Escherichia coli* ATCC 25922 and *Escherichia coli* NCTC 13846 (mcr-1-positive) were used as quality control strains.

Statistical Analyses

Categorical variables are reported as n (percentages); continuous variables with a normal distribution are expressed as means ± standard deviations (SD); and continuous variables with a non-normal distribution are described as medians (interquartile ranges: IQRs). Categorical data were analyzed using chi-squared or Fisher's exact tests; the Student's *t*-test or the Mann–Whitney *U*-test was used to analyze continuous variables. Odds ratios (ORs) with 95% confidence intervals (CIs) and P-values were used for univariate analyses. Variables with a P–value < 0.05 in the univariate analyses were entered into multivariate logistic regression. Survival curves (150 day) were created using the Kaplan–Meier method. Log rank tests were performed using Prism 8.0 (GraphPad). Other statistical analyses were performed using SPSS (version 25.0; IBM Corporation, Armonk, NY, USA). P < 0.05 was considered statistically significant.

Results

Characteristics of PR Isolates

As shown in Figure 1, the most commonly identified PR *Enterobacterales* was *K. pneumoniae* (72.2%; 52/72), followed by *Salmonella enteritidis* (8.3%; 6/72), and *Escherichia coli* (5.6%; 4/72). Among the PR isolates, 34.7% (25/72) were isolated from sputum and BALF, 22.2% (16/72) from urine, 20.8% (15/72) from blood, and the remainder from other samples.

Antimicrobial susceptibility testing revealed that the resistance rate for 52 *K. pneumoniae* isolates was significantly higher than that of the other 20 *Enterobacterales* isolates. In particular, 76.9% (40/52) of *K. pneumoniae* isolates were carbapenem-resistant (Figure 2).

Patient Characteristics

A total of 72 patients carrying PR *Enterobacterales* were included during the 5-year study period, and 144 patients carrying PS *Enterobacterales* were included as controls. The median ages of cases and controls were 63 (51–73) and 62 (48–73) years, respectively (P = 0.391), and 66.67% of patients were male. Of the study patients, 63.89% were admitted to the ICU. Patient characteristics are shown in Table 1.

Risk Factors for Isolation with PR Strains

Table 1 compares the clinical characteristics of patients with PR and PS controls. Univariate analysis revealed that chronic heart disease, chronic kidney disease, organ transplantation, immunosuppressant use, invasive procedures (central venous catheter, chest drainage tube [chest], and head drainage tube [head]), and polymyxin B exposure were associated with the isolation of PR *Enterobacterales*.

Chronic heart disease (P = 0.012; odds ratio [OR] 1.15; 95% confidence interval [CI] 1.03–1.28), immunosuppressant use (P = 0.016; OR 1.04 [1.0–1.07]), drainage tube [head] (P = 0.006; OR 1.1 [1.0–1.1]), and polymyxin B exposure (P = 0.007; OR 1.03 [1.0–1.06]) were independently related to the isolation of PR *Enterobacterales* in a multivariate analysis (Table 1).

Treatment Failure Among Cases and Controls

Among the 72 patient cases, 33 (45.83%) experienced treatment failure; Conversely, within the cohort of 144 controls, 21 (14.58%) experienced treatment failure. The survival rate was significantly lower in patients in the case group than in the control group in the survival curve analysis (Figure 3).

Univariate analyses revealed that a history of ICU admission, hypertension, nervous system disease, mechanical ventilation, urinary catheter, central venous catheter, and head drainage were associated with treatment failure (Table 2). In

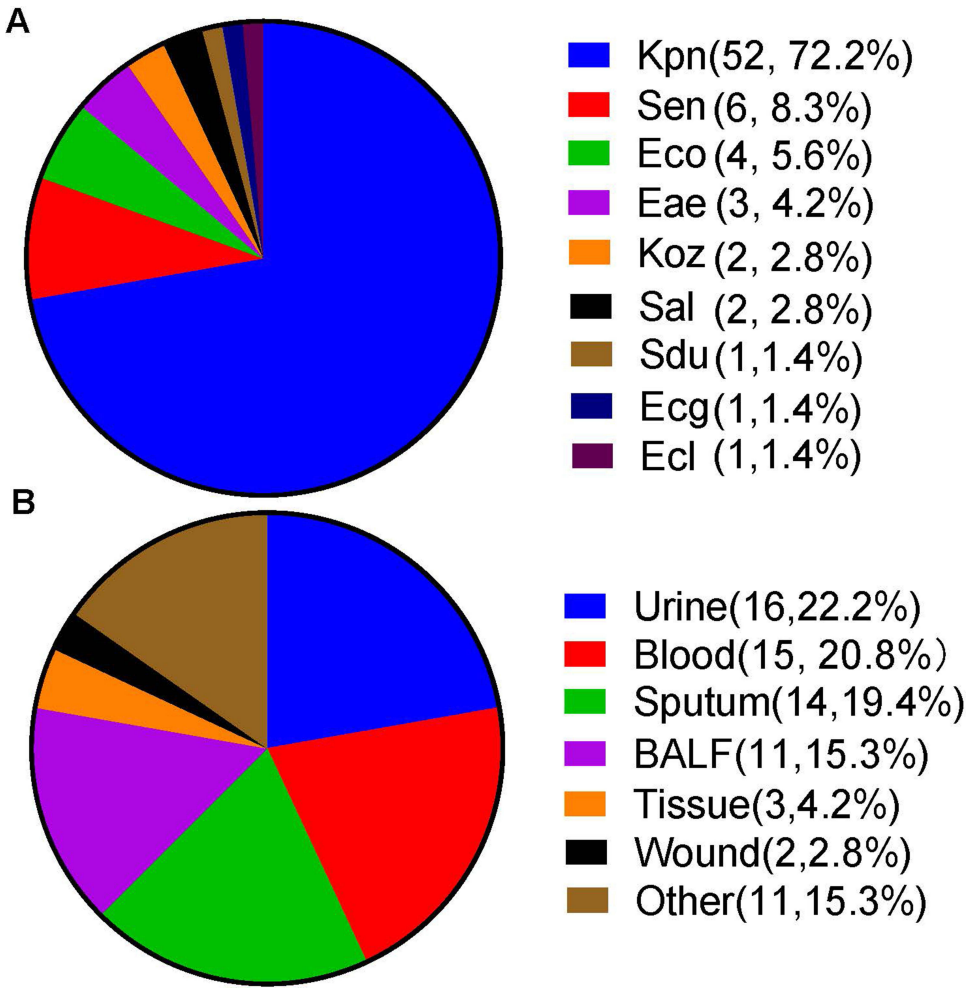

Figure 1 Types (**A**) and sample sources (**B**) of polymyxin B-resistant *Enterobacterales*.
Abbreviations: Kpn, *Klebsiella pneumoniae*; Sen, *Salmonella enteritidis*; Eco:, *Escherichia coli*; Eae, *Klebsiella aerogenes*; Koz, *Klebsiella ozaenae*; Sal, *Salmonella spp.*; Sdu, *Salmonella Dublin*; Ecg, *Enterobacter cancerogenus*; Ecl, *Enterobacter cloacae*; BALF, Bronchoalveolar lavage fluid.

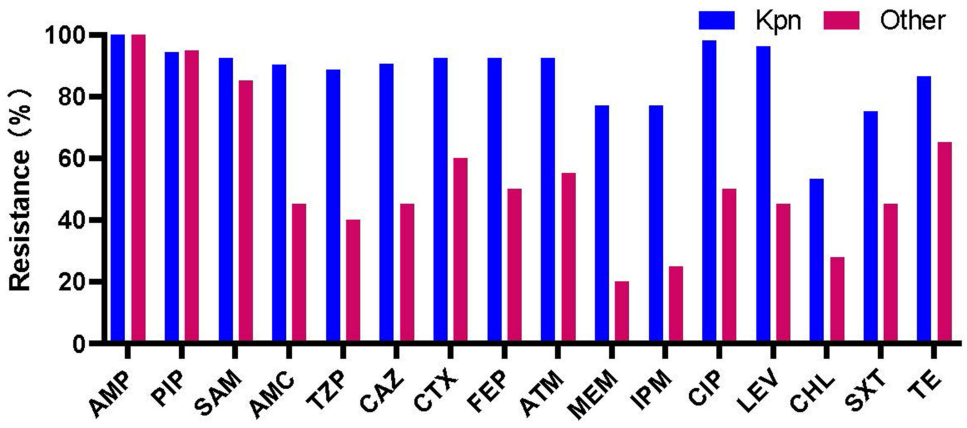

Figure 2 Comparison of antibiotic resistance percentages between 52 strains of polymyxin B-resistant *Klebsiella pneumoniae* and 20 strains of other *Enterobacterales*.
Abbreviations: AMP, ampicillin; PIP, piperacillin; SAM, ampicillin-sulbactam; AMC, amoxicillin-clavulanic acid; TZP, piperacillin-tazobactam; CAZ, ceftazidime; CTX, cefotaxime; FEP, cefepime; ATM, aztreonam; MEM, meropenem; IPM, imipenem; CIP, ciprofloxacin; LEV, levofloxacin; CHL, chloramphenicol; SXT, trimethoprim sulfamethoxazole; TE, tetracycline.

Table 1 Univariate and Multivariate Analyses of Risk Factors in Patients Infected with Polymyxin-Resistant *Enterobacterales* Strains

Characteristic	Cases (n =72) n%	Controls (n = 144) n%	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	p–value	OR (95% CI)	P–value
Basic Information						
Male	48 (66.67)	90 (62.50)	1.1 (0.8–1.7)	0.548		
History of hospital transfers	46 (63.89)	87 (60.42)	1.1 (0.8–1.6)	0.664		
Admission to an ICU	46 (63.89)	84 (58.33)	1.2 (0.8–1.7)	0.432		
History of department transfers	34 (47.22)	57 (39.58)	1.1 (0.9–1.5)	0.284		
Comorbidities						
Smoking history	24 (33.33)	54 (37.50)	1.1 (0.8–1.7)	0.548		
Alcoholism	15 (20.83)	42 (29.17)	1.4 (0.8–2.3)	0.190		
Diabetes mellitus	23 (31.94)	52 (36.11)	1.1 (0.8–1.7)	0.544		
Hypertension	27 (37.50)	58 (40.28)	1.1 (0.8–1.5)	0.694		
Decubitus ulcers	8 (11.11)	15 (10.42)	1.1 (0.9–1.1)	0.889		
Pulmonary disease	30 (41.67)	48 (33.33)	1.1 (0.9–1.5)	0.229		
Chronic heart failure	19 (26.39)	21 (14.58)	2.1 (1.0–4.2)	0.035	1.15 (1.03–1.28)	0.012
Chronic renal failure	13 (18.06)	10 (6.94)	2.9 (1.2–7.1)	0.013		
Chronic liver disease	14 (19.44)	18 (12.50)	1.7 (0.8–3.6)	0.176		
Neurological disease	16 (22.22)	27 (18.75)	1.2 (0.6–2.5)	0.547		
Tumour	8 (11.11)	22 (15.28)	0.7 (0.3–1.6)	0.404		
Hematologic diseases	10 (13.89)	11 (7.64)	2.0 (0.8–4.8)	0.144		
Organ transplantation	3 (4.17)	0 (0.00)	1.1 (1.0–1.1)	0.014		
Digestive diseases	8 (11.11)	12 (8.33)	1.4 (0.5–3.5)	0.507		
Invasive Procedures						
Mechanical ventilation	42 (58.33)	70 (48.61)	1.5 (0.8–2.6)	0.178		
Previous surgery	50 (69.44)	83 (57.64)	1.7 (0.9–3.0)	0.093		
Central venous catheter	52 (72.22)	80 (55.56)	2.1 (1.1–3.8)	0.018		
Urinary catheter	48 (66.67)	98 (68.06)	0.9 (0.5–1.7)	0.837		
Use of immunosuppressive agents	45 (62.5)	69 (47.92)	1.8 (1.0–3.2)	0.048	1.04 (1.0–1.07)	0.016
Haemodialysis	11 (15.28)	17 (11.81)	1.3 (0.6–3.1)	0.474		
Nasogastric tube	37 (51.39)	71 (49.31)	1.1 (0.6–1.9)	0.773		
Chest drainage	16 (22.22)	15 (10.42)	2.5 (1.1–5.3)	0.02		
Head drainage	11 (15.28)	8 (5.56)	3.1 (1.1–8.0)	0.017	1.1 (1.0–1.1)	0.006
Abdominal drainage	15 (20.83)	30 (20.83)	1.5 (0.5–2.0)	0.99		
Antibiotic Exposure						
Aminoglycosides	9 (12.50)	14 (9.72)	1.3 (0.5–3.2)	0.533		
Beta–lactam–beta–lactamase inhibitors	25 (34.72)	48 (33.33)	1.1 (0.6–2.0)	0.839		
Carbapenem	48 (66.67)	86 (59.72)	1.4 (0.8–2.6)	0.233		
Cephalosporin	33 (45.83)	56 (38.89)	1.3 (0.7–2.3)	0.349		
Polymyxins	18 (25.00)	15 (10.42)	2.9 (1.3–6.1)	0.005	1.03 (1.0–1.06)	0.007

Abbreviations: ICU, intensive care unit; OR, odds ratio.

multivariate analysis, independent risk factors for treatment failure included admission to an ICU (P = 0.003; OR 7.1 [1.9–25.4]), hypertension (P = 0.035; OR 1.4 [1.02–1.83]), and drainage tube [head] (P = 0.044; OR 1.1 [1.0–1.15]) (Table 2).

Discussion

Increased polymyxin consumption for multidrug-resistant Gram-negative bacilli treatment has resulted in the development of polymyxin B resistance by these species in several countries.[20] This is an important public health issue. Monitoring the resistance mechanism and elucidating risk factors for polymyxin B resistance may be helpful for preventing the spread of resistant strains.

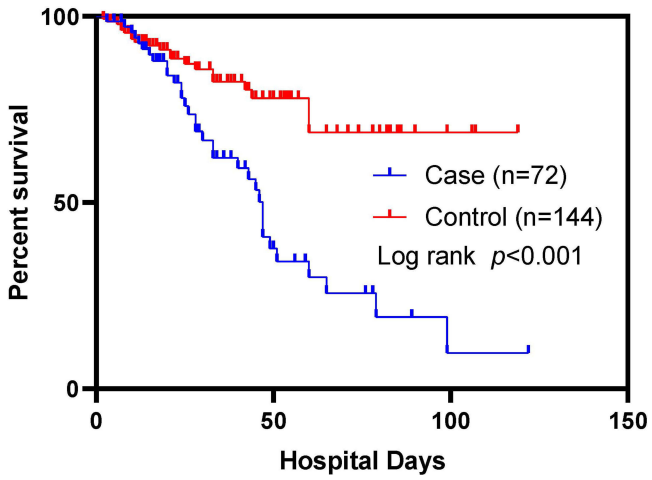

Figure 3 Survival curves between patients with (case) and without (control) polymyxin B-resistant *Enterobacterales* isolation.

In this study, the most common PR *Enterobacterales* was *K. pneumoniae* (72.2%), consistent with previous results.[16,21,22] Additionally, 76.9% (40/52) of PR *K. pneumoniae* isolates were carbapenem resistant. The resistance rates of carbapenem-resistant *K. pneumoniae* to colistin in Taiwan[21] and Oman[23] were 17% and 24.2%, respectively. We found that polymyxin B exposure is a risk factor for hospitalized patients with PR *Enterobacterales*, which is consistent with the results of previous studies.[24,25] However, most of the prior literature focuses on PR combined with carbapenem resistance and/or specific populations, such as critically ill patients, or specific infection types, such as bloodstream infection (BSI). For example, previous polymyxin B exposure was a predictor of the isolation of PR carbapenem-resistant and carbapenemase-producing *Enterobacterales* or colistin-resistant *K. pneumoniae* in other studies.[15,24] Colistin was reported to be related to the development of colistin-resistant *K. pneumoniae* BSI.[26] In another study, recent exposure to colistin or polymyxin B was related to increased opportunities for colistin resistance.[27] Except for polymyxin B exposure and carbapenem resistance, previous exposure to carbapenems was the risk factor for colonization or infection with PR *E. coli* or *K. pneumoniae* in a low-endemicity setting.[17]

Table 2 Univariate and Multivariate Analyses of Risk Factors for Treatment Failure in Patients with Polymyxin B-Resistant *Enterobacterales* Infection

Characteristic	Treatment Success (n = 39), n%	Treatment Failure (n = 33), n%	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P–value	OR (95% CI)	P–value
Basic Information						
Male	23 (58.97)	25 (75.76)	0.4 (0.2–1.3)	0.132		
History of hospital transfers	23 (58.97)	23 (69.70)	1.9 (0.6–4.3)	0.345		
Admission to an ICU	17 (43.59)	29 (87.88)	9.4 (2.8–31.9)	0.001	7.1 (1.9–25.4)	0.003
History of department transfers	18 (46.15)	16 (48.48)	1.1 (0.4–2.8)	0.844		
Comorbidities						
Smoking history	12 (30.77)	12 (36.36)	1.3 (0.5–3.4)	0.616		
Alcoholism	6 (15.38)	9 (27.27)	2.1 (0.6–6.6)	0.216		
Diabetes mellitus	12 (30.77)	11 (33.33)	1.1 (0.4–3.0)	0.816		
Hypertension	10 (25.64)	17 (51.52)	3.1 (1.1–8.3)	0.024	1.4 (1.02–1.83)	0.035
Decubitus ulcers	2 (5.13)	6 (18.18)	4.1 (0.8–21.9)	0.079		
Pulmonary disease	13 (33.33)	17 (51.52)	2.1 (0.8–5.5)	0.119		
Chronic heart failure	7 (17.95)	12 (36.36)	2.6 (0.9–7.7)	0.077		
Chronic renal failure	6 (15.38)	7 (21.21)	1.5 (0.4–4.9)	0.522		

(*Continued*)

Table 2 (Continued).

Characteristic	Treatment Success (n = 39), n%	Treatment Failure (n = 33), n%	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P–value	OR (95% CI)	P–value
Chronic liver disease	7 (17.95)	7 (21.21)	1.2 (0.4–3.9)	0.727		
Neurological disease	5 (12.82)	11 (33.33)	3.4 (1.1–11.1)	0.037		
Tumour	4 (10.26)	4 (12.12)	1.2 (0.3–5.3)	0.802		
Hematologic diseases	6 (15.38)	4 (12.12)	0.8 (0.2–3.0)	0.955		
Organ transplantation	2 (5.13)	1 (3.03)	0.6 (0.1–6.7)	0.657		
Digestive diseases	4 (10.26)	4 (12.12)	1.2 (0.3–5.3)	0.99		
Invasive Procedures						
Mechanical ventilation	16 (41.03)	26 (78.79)	5.3 (1.9–15.3)	0.001		
Previous Surgery	24 (61.54)	26 (78.79)	2.3 (0.9–2.7)	0.113		
Central venous catheter	19 (48.72)	26 (78.79)	1.4 (1.1–1.7)	0.006		
Urinary catheter	21 (53.85)	27 (81.82)	3.9 (1.3–11.4)	0.012		
Use of immunosuppressive agents	23 (58.97)	22 (66.67)	1.4 (0.5–3.7)	0.502		
Haemodialysis	4 (10.26)	7 (21.21)	1.9 (0.6–8.9)	0.198		
Nasogastric tube	17 (43.59)	20 (60.61)	2.0 (0.8–5.1)	0.150		
Chest drainage	9 (23.08)	7 (21.21)	0.9 (0.3–2.7)	0.850		
Head drainage	2 (5.13)	9 (27.27)	6.9 (1.4–34.9)	0.009	1.1 (1.0–1.15)	0.044
Abdominal drainage	8 (20.51)	7 (21.21)	1.0 (0.3–3.3)	0.999		
Antibiotic Exposure						
Aminoglycosides	5 (12.82)	4 (12.12)	0.9 (0.2–3.8)	0.954		
Beta–lactam–beta–lactamase inhibitors	10 (25.64)	15 (45.45)	2.4 (0.9–6.5)	0.078		
Carbapenem	24 (61.54)	25 (75.76)	2.0 (0.7–5.4)	0.197		
Cephalosporin	19 (48.72)	14 (42.42)	0.8 (0.3–2.0)	0.593		
Quinolone	8 (20.51)	7 (21.21)	1.0 (0.3–3.3)	0.942		
Polymyxins	7 (17.95)	11 (33.33)	2.3 (0.8–6.8)	0.133		

Abbreviations: ICU, intensive care unit; OR, odds ratio.

Chronic heart failure, use of immunosuppressive agents, and head drainage were also risk factors for PR *Enterobacterales* in our study population. It was reported that coronary heart disease is an independent risk factor that predisposes patients to PR resistance.[28] Chronic renal failure has been shown as a risk factor in critically ill patients with PR and carbapenemase-producing *Enterobacterales* in a previous study, which also included other risk factors such as surgical procedures, indwelling devices (urinary catheters), and transfer between hospital wards.[16] Other risk factors associated with colistin resistance in Gram-negative bacilli include neurological disease, residence in a nursing facility prior to admission, receipt of carbapenems or an antimicrobial with anti-methicillin-resistant *Staphylococcus aureus* activity, and receipt of ventilatory support.[4] In addition, male sex, immunosuppression, and antibiotic use, particularly carbapenems and fluoroquinolones, are associated with mcr-1-positive *E. coli* infection.[29] Increased age (> 55 years) and antibiotic use in the preceding 90 days were associated with an increased risk in patients with colistin-resistant *Enterobacterales*.[30]

Regarding patient outcomes, our study demonstrated that the rate of treatment failure in 72 patients carrying PR strains was 45.83%, which is similar to previous results that reported an overall mortality of between 35% and 66%.[16,17,22,31] In bloodstream infections caused by carbapenem-resistant *K. pneumoniae*, age and colistin resistance increased the 28-day mortality.[32] In our study, multivariate regression analysis showed that ICU admission, hypertension, and head drainage were associated with treatment failure, different from a previous study that reported that carbapenem exposure was associated with mortality among adult ICU patients with PR *Enterobacterales* strains.[16]

This study has some limitations. First, the retrospective and single-centre research design could result in selection biases. Second, the association between possible risk factors identified in this study and the isolation of PR strains was

only a statistical link and needs to be validated using more samples. Third, we did not evaluate resistance mechanisms in the PR strains. Thus, more surveillance and multicenter studies are required.

Conclusions

In conclusion, this study revealed that the common bacteria resistant to polymyxin B in Henan, China, are *K. pneumoniae, S. enteritidis*, and *E. coli*, and that more than half of *K. pneumoniae* are also resistant to carbapenem. Risk factor analysis showed that chronic heart failure, use of immunosuppressive agents, head drainage, and polymyxin B exposure are related to the acquisition of PR strains. ICU admission, hypertension, and head drainage are associated with treatment failure. Therefore, hospitals should take multiple measures to prevent further outbreaks of PR *Enterobacterales*.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was conducted with the approval of the Ethics Committee of the Henan Provincial People's Hospital (2022-1-233). All organs for transplant recipients were given freely and with written informed consent. Additionally, the donation and transplantation processes follow the guidelines of the Declaration of Istanbul.

Additionally, the Ethics Committee of Henan Provincial People's Hospital granted a waiver for patient consent, given that the study neither involved the collection of personal information nor subjected participants to any interventions. The study was conducted in accordance with the Declaration of Helsinki, data were anonymized, and the confidentiality of patients was guaranteed.

Author Contributions

All authors made a significant contribution to the work reported in the conception, study design, execution, acquisition of data, analysis, and interpretation. All authors took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, and have agreed on the journal to which the article has been submitted. All authors agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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