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ORIGINAL RESEARCH

Clinical and Antibiotic Resistance Features for Extended-Spectrum Betalactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* Bloodstream Infections and Predictors of Poor Prognosis in Neonatal Patients

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Background: Neonatal bloodstream infections (BSIs) caused by extended-spectrum β-lactamase *Enterobacterales* (ESBL-E) are associated with high rates of morbidity and mortality. This study aimed to describe the clinical characteristics, profiles of antibiotic susceptibility, and risk factors associated with BSIs caused by *E. coli* (ESBL-EC) and *K. pneumoniae* (ESBL-KP), and identify risk factors for poor prognosis in neonatal patients with *E. coli* or *K. pneumoniae* BSIs.

Methods: In the period from January 2017 to December 2023, a retrospective case-control study was conducted at Guangxi Children's Hospital in China. Demographic, clinical, and microbiological characteristics were collected. Antimicrobial resistance (AMR) profiles and clinical risk factors associated with ESBL-EC and ESBL-KP BSIs were systematically evaluated, along with independent predictors of poor prognosis in neonates with ESBL-EC or ESBL-KP BSIs.

Results: A total of 139 patients with *E. coli* and *K. pneumoniae* BSIs were enrolled, comprising 29 patients with ESBL-EC, 13 patients with ESBL KP, 10 patients with carbapenem-resistant *K. pneumoniae* (CRKP), and 87 patients with non-ESBL strains of BSIs. ESBL-EC and ESBL-KP demonstrated elevated resistance rates to the majority of clinically commonly used antibiotics. Late premature infant, very low birth weight, cesarean section, pneumonia, and mechanical ventilation were associated with the development of ESBL strains BSIs. Furthermore, very premature infants, extremely low birth weight, hypoalbuminemia, anemia, and isolation of CRKP were significantly correlated with a poor prognosis. Hypoalbuminemia (OR: 3.922, 95% CI: 1.189–12.937, p=0.025) and the isolation of CRKP (OR: 11.548, 95% CI: 1.785–74.708, p=0.010) were independent predictors of poor prognosis for *E. coli* and *K. pneumoniae* BSIs in neonatal patients.

Conclusion: Late premature infant, very low birth weight, cesarean section, pneumonia, and mechanical ventilation were associated with the development of ESBL strains BSI. More attention should be paid to ESBL strains causing BSI in the neonatal population.

Keywords: neonatal, BSI, risk factor, ESBL

Introduction

Bloodstream infection (BSI) is a severe and often fatal complication linked to accelerated morbidity and mortality, with an annual incidence ranging from 150 to 309 cases per 100,000 population and a mortality rate ranging from 12.5% to 22.7.[1–3] Neonates, in particular, face even higher risks and mortality rates of BSIs, with a mortality rate ranging from 19.7% to 30%.[4–6] *Escherichia coli* (*E. coli*) and *Klebsiella pneumonia* (*K. pneumoniae*) stand as prominent pathogens responsible for neonatal BSIs, with significant mortality rates linked to their infectious impact, presenting a formidable

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obstacle to anti-infective treatment.[6,7] Therefore, it is crucial in clinical practice to identify predictors associated with poor prognosis in *E. coli* and *K. pneumoniae* neonatal BSIs.

The emergence of antimicrobial resistance (AMR), particularly in extended-spectrum β-lactamase (ESBL)-producing bacteria, constitutes a significant global health challenge. This is primarily due to its frequent association with the failure of empirical antibiotic therapy, leading to elevated morbidity and mortality rates.[8] In 2019, an estimated 4.95 million deaths were associated with bacterial AMR, among which 1.27 million were attributable to bacterial AMR.[9] ESBL is a Gram-negative bacterium of the Enterobacteriaceae family, which harbors ESBL genes either within its plasmids or integrated into its chromosomal DNA.[10] It produces β-lactam hydrolyzing enzymes, providing resistance to penicillin, aztreonam, and first-, second-, and third-generation cephalosporins, while lacking the ability to hydrolyze carbapenems or cephamycin.[11] Among a wide range of Gram-negative bacteria harboring ESBL genes, *E. coli* (ESBL-EC) and *K. pneumoniae* (ESBL-KP) are the most common hosts, causing infections such as BSIs, urinary tract infections, and diarrhea, particularly among neonates, in both hospital and community settings.[12–14] Although our previous research demonstrated a notably high prevalence of *K. pneumoniae* infections among preterm neonates, coupled with suboptimal treatment outcomes and elevated antimicrobial resistance patterns,[15] the existing literature on ESBL-EC and ESBL-KP neonatal bloodstream infections remains scarce. Significant knowledge gaps persist regarding their clinical manifestations, epidemiological characteristics, and antimicrobial resistance profiles. Addressing these gaps is critical for developing targeted strategies to mitigate the impact of ESBL-EC and ESBL-KP neonatal BSIs.

The present study aims to bridge this knowledge gap by systematically investigating the clinical features and antimicrobial resistance profiles of ESBL-EC and ESBL-KP. Through analyzing clinical data, AMR patterns, and the production of ESBL, this research seeks to enhance our understanding of these pathogens, and facilitate the development of evidence-based containment strategies and optimized therapeutic interventions.

Methods

Study Setting and Patients

We conducted a retrospective cohort study from January 2017 to December 2023 at the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, which is the largest children's hospital in the region. During the study period, 180,297 blood culture tests were conducted, with a positivity rate of 1.88% (3394/180,297). In this study we focused on cases of BSIs caused by E. coli and K. pneumoniae in diagnosed patients. For each patient, only the first *E. coli* or *K. pneumoniae* BSI isolate was selected for analysis. The inclusion criteria were defined as follows: (a) patients aged 28 days or younger, (b) meets criteria indicative of neonatal bloodstream infections,[16] (c) a positive blood culture for *E. coli* or K. *pneumonia*, (d) hospitalization with complete clinical data available. Conversely, the analysis systematically excluded outpatients with incomplete or unavailable medical records. The protocol for this study was approved by the research administration of Medical Ethics Committee of Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region (No. 2023-3-42). This study used an anonymous method to protect the participants and obtained their permission.

Data Collection and Definitions

Various clinical features of the enrolled patients were collected from the hospital's electronic health records system. The collected data encompassed essential demographic information (gender, gestational age, and weight), medical history (underlying diseases, cesarean sections, premature ruptures of membrane), interventions (invasive procedures and devices, antibiotic exposure), bloodstream infection type and outcomes.

According to the gestational age at birth, neonates can be classified as follows: term infants, with a gestational age of 37 weeks or more to 42 weeks; late premature infants, with a gestational age between 28 weeks and 37 weeks; and extremely preterm infants, with a gestational age between 22 weeks and 28 weeks. Based on the weight at birth, newborns can be categorized as follows: extremely low birth weight (ELBW) denotes infants with a birth weight below 1000g; very low birth weight (VLBW) indicates infants with a birth weight ranging from 1000g to under 1500g; low birth weight (LBW) signifies infants with a birth weight between 1500g to less than 2500g; normal birth weight (NBW) pertains to infants with a birth weight between 2500g to 4000g; macrosomia describes infants with a birth weight

exceeding 4000g. Hypoalbuminemia is generally defined as a serum albumin level of less than 35 g/L. Anemia refers to a peripheral hemoglobin (Hb) concentration of less than 120 g/L. Treatment outcomes were divided into two distinct groups based on clinical documentation. Patients who achieved clinical recovery or showed significant improvement upon discharge were classified as having a favorable prognosis, while those who died during hospitalization or were discharged in critical condition were classified as having a poor prognosis.

Microbiological Methods

In this investigation, all intentionally collected isolates were cultivated on blood agar plates at 37 °C in an incubator for 18–24 hours. The isolates were then identified using the Zhuhai DL-96IIautomatic bacterial identification drug sensitivity apparatus (Zhuhai DL Biotech Co., Ltd.,China) or the VITEK2 Compact system (BioMérieux, Marcy l'Etoile, France). The antibiotic susceptibility tests were performed on the isolates utilizing either the Kirby-Bauer methodology, the Zhuhai DL-96II automated bacterial identification drug sensitivity apparatus or the VITEK 2 Compact system. Each protocol was carried out according to the manufacturer's guidelines. The minimum inhibitory concentrations (MICs) of common clinical antibiotics, including gentamicin, sulfamethoxazole, ciprofloxacin, ceftazidime, cefazolin, cefepime, meropenem, piperacillin-tazobactam, imipenem, amikacin, ampicillin-sulbactam, ceftriaxone, ticarcillin-clavulanic acid, chloramphenicol, amoxicillin, cefuroxime, minocycline, levofloxacin, and cefoxitin. The findings were elucidated in accordance with the protocols delineated by the Clinical and Laboratory Standards Institute M100 document, and ESBL screen was determined based on the susceptibility test for ceftriaxone and ceftazidime (MIC $\geq$ 2 μg/mL), excluding carbapenem-resistant strains.

The confirmation of ESBL-producing isolates was conducted using the combination broth microdilution. A comparison of the MIC was made between ceftazidime and cefotaxime alone versus those of ceftazidime and cefotaxime containing clavulanic acid. Following the designated incubation period, a reduction of ≥3-fold in the minimum inhibitory concentration (MIC) of any antimicrobial agent when tested in combination with clavulanate, compared to its MIC value when tested independently, was identified as indicative of ESBL production, in accordance with the criteria established by the Clinical and Laboratory Standards Institute (CLSI). The quality control strains employed were *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 (National Center for Clinical Laboratories, Beijing, China).

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Count data were reported as percentages, and group comparisons were performed using $\chi 2$ tests or Fisher's exact test for categorical variables. Variables that showed significance ($p<0.10$) in the univariate analysis, including extremely low birth weight, very premature infants, anemia, hypoalbuminemia, CRKP, mechanical ventilation, and central venous catheterization, were selected for inclusion in a logistic regression model to evaluate their association with poor Prognosis. Statistical significance was considered at p-values less than 0.05.

Results

Baseline Characteristics of 139 Neonates with *Escherichia coli* and *Klebsiella pneumoniae* Bloodstream Infections

During the study period, a total of 139 unique cases of neonatal BSIs caused by *E. coli* and *K. pneumoniae* were identified. Of these, 29 BSIs were caused by ESBL-EC (20.8%), 13 by ESBL KP (9.3%), 87 by non-ESBL strains, and 10 by CRKP (7.1%). Among the participants, 74 (53.2%) were male. The majority of neonates included in the study were term infants (50.4%) and normal birth weights (48.9%). Most of them developed late-Onset infections (66.2%) and breast-fed (70.5%). The most underlying diseases was hypoalbuminemia (35.9%), while the invasive procedures and devices was mechanical ventilation (53.2%), respectively. The predominant antibiotic exposures was β-lactam-β-lactamase inhibitors (31.6%). 26 (18.7%) neonates with poor prognosis were hospitalized after the onset of *E. coli* and *K. pneumoniae* bloodstream infections (Supplementary Table 1).

Microbiological Characteristics of *Escherichia coli* and *Klebsiella pneumoniae* Isolates

Among the 139 isolates, 95 were *E. coli* and 44 were *K. pneumoniae*. All strains have completed antimicrobial susceptibility testing, and the drug resistance profiles are shown in Table 1. Among *Escherichia coli* strains, the three antimicrobial agents with the highest resistance rates were ampicillin (82.1%), sulfamethoxazole (65.2%), and cefazolin (44.2%). Notably, no strains exhibited resistance to carbapenems. In comparison, the resistance rates of ampicillin (*P*=0.003), ceftazidime (*P*=0.015), ceftriaxone (*P*=0.000), cefepime (*P*=0.000), cefuroxime (*P*=0.000), cefazolin (*P*=0.000), ciprofloxacin (*P*=0.000), levofloxacin (*P*=0.01) and minocycline (*P*=0.031) were significantly higher in the ESBL-EC strains than non- ESBL-EC strains.

Meanwhile, the resistance rates of K. pneumoniae to ampicillin, cefuroxime, cefazolin, and ceftriaxone are alarmingly high, standing at 100.00%, 54.5%, 54.5%, and 50.00%, respectively. Furthermore, the resistance rates for imipenem and meropenem exceed 20%, specifically standing at 22.7%. In contrast to non-ESBL-KP, ESBL-KP exhibited an elevated level of resistance towards ampicillin-sulbactam (*P*=0.000), ceftriaxone (*P*=0.000), cefepime (*P*=0.000), cefuroxime (*P*=0.000), cefazolin (*P*=0.000), ciprofloxacin (*P*=0.000), chloramphenicol (*P*=0.000), gentamicin (*P*=0.001), levofloxacin (*P*=0.001), sulfamethoxazole (*P*=0.000), and ticarcillin-clavulanic acid (*P*=0.000).

Risk Factors Associated with Bloodstream Infections Caused by ESBL-Producing Strains

Among 139 patients analyzed, 42 (30.2%) BSIs were attributed to ESBL strains, while 87 (62.6%) were caused by non-ESBL strains. Notably, 10 cases (7.2%) involved CRKP strains. Comparative analysis of demographic, and clinical parameters between patients with ESBL-producing and non-ESBL BSIs is presented in Table 2. The factors most significantly associated with ESBL strains bloodstream infections in neonates were late premature infant (*P*=0.037), very low birth weight (*p*=0.001), cesarean section (*p*=0.003), pneumonia (*P*=0.037), mechanical ventilation (*p*=0.000), and length of hospital stay >30 days (*p*=0.001). In

Table 1 Antibiotic Susceptibility Profiles for *Escherichia coli* and *Klebsiella pneumoniae* Isolates

Antibiotic	Resistant No. (%) of *Escherichia coli*			Resistant No. (%) of *Klebsiella pneumoniae*		
	ESBL-EC (n=29)	Non-ESBL-EC (n=66)	P-value	ESBL-KP (n=13)	Non-ESBL-KP (n=21)	*P*-value
Ampicillin	29(100)	49(74.2)	**0.003**	13(100)	21(100)	–
Ampicillin-sulbactam	1(3.4)	12(18.1)	0.054	10(76.9)	1(4.7)	**0.000**
Ceftazidime	5(17.2)	2(3.0)	**0.015**	2(15.3)	1(4.7)	0.289
Ceftriaxone	29(100)	8(12.1)	**0.000**	11(84.6)	1(4.7)	**0.000**
Cefepime	10(34.4)	3(4.5)	**0.000**	8(61.5)	0	**0.000**
Cefuroxime	29(100)	8(12.1)	**0.000**	12(92.3)	2(9.5)	**0.000**
Cefazolin	29(100)	13(19.6)	**0.000**	12(92.3)	2(9.5)	**0.000**
Cefoxitin	0	1(1.5)	0.505	2(15.3)	2(9.5)	0.606
Ciprofloxacin	18(62.0)	13(19.6)	**0.000**	9(69.2)	0	**0.000**
Chloramphenicol	9(31.0)	11(16.6)	0.114	10(76.9)	1(4.7)	**0.000**
Gentamicin	10(34.4)	13(19.6)	0.121	6(46.1)	0	**0.001**
Levofloxacin	13(44.8)	9(13.6)	**0.001**	6(46.1)	0	**0.001**
Minocycline	2(6.8)	0	**0.031**	3(23.0)	1(4.7)	0.107
Piperacillin-tazobactam	0	1(1.5)	0.505	–	–	–
Sulfamethoxazole	22(75.8)	40(60.6)	0.150	11(84.6)	3(14.2)	**0.000**
Ticarcillin-clavulanic acid	0	2(3.0)	0.392	6(46.1)	0	**0.000**
Amikacin	–	–	–	0	1(4.7)	0.425
Imipenem	–	–	–	–	–	–
Meropenem	–	–	–	–	–	–

Notes: Bold represents p<0.05. –: not detected.
Abbreviations: ESBL-EC, extended-spectrum β-lactamase *Escherichia coli*; ESBL-KP, extended-spectrum β-lactamase *Klebsiella pneumonia*.

Table 2 Comparison of Neonatal Variables Between Those with BSIs Caused by ESBL and Non-ESBL Strains

Factors	ESBL (n=42)	Non-ESBL (n=87)	*P*-value
Basic data			
Gender (male) n(%)	27(64.2)	44(50.5)	0.142
Term infant n(%)	16(38.1)	54(62.0)	**0.010**
Late premature infant n(%)	21(50.0)	37(31.1)	**0.037**
Very premature infants n(%)	5(11.9)	6(6.9)	0.340
Normal birth weight n(%)	16(38.1)	52(59.7)	**0.021**
Low birth weight n(%)	10(23.8)	24(26.6)	0.855
Very low birth weight n(%)	13(30.9)	7(8.0)	**0.001**
Extremely low birth weight n(%)	3(7.2)	5(5.7)	0.758
Early-Onset infection n(%)	16(38.1)	31(35.6)	0.785
Cesarean section n(%)	24(57.1)	26(29.8)	**0.003**
Premature rupture of membrane n(%)	23(54.7)	35(40.2)	0.120
Breast-fed n(%)	27(64.2)	64(73.5)	0.279
Underlying diseases			
Pneumonia n(%)	12(28.5)	11(12.6)	**0.027**
Enteritis n(%)	1(2.3)	7(8.0)	0.398
Neonatal meningitis n(%)	2(4.7)	6(6.8)	0.638
Hypoalbuminemia n(%)	15(35.7)	26(29.8)	0.505
Anemia n(%)	9(21.4)	24(27.5)	0.453
Invasive procedures and devices			
Mechanical ventilation n(%)	31(73.8)	33(37.9)	**0.000**
Indwelling catheters n(%)	3(7.1)	3(3.4)	0.350
Central venous catheterization n(%)	3(7.1)	6(6.8)	0.959
Antibiotic exposure			
Penicillins n(%)	3(4.7)	4(4.5)	0.967
Cephalosporins n(%)	5(11.9)	6(6.8)	0.340
Carbapenem antibiotic n(%)	4(9.5)	7(8.0)	0.788
β-lactam-β-lactamase inhibitors n(%)	15(35.7)	21(24.1)	0.170
Outcomes			
Poor prognosis n(%)	4(9.6)	15(17.3)	0.246
Length of hospital stay (>30 days) n(%)	21(50.0)	18(20.6)	**0.001**

Note: Bold represents p<0.05.
Abbreviation: ESBL, extended-spectrum β-lactamase.

contrast, term infants (p=0.010) and normal birth weight infants (P=0.021) were more prevalent in the non-ESBL strains group than in the ESBL strains group.

Additionally, the comparison of patient variables between individuals with BSIs due to ESBL *E. coli* and those with BSIs due to non-ESBL *E. coli* showed that cesarean section (p=0.031), pneumonia (P=0.041), mechanical ventilation (p=0.014), indwelling catheters (p=0.048) and length of hospital stay >30 days (p=0.012) were more associated with ESBL *E. coli* BSIs (Table 3).

Furthermore, the analysis of patient characteristics in individuals suffering from BSIs caused by ESBL-producing *K. pneumoniae* compared to those with infections caused by non-ESBL-producing *K. pneumoniae* revealed that late premature infants (p=0.031), very low birth weight (p=0.004), and mechanical ventilation (p=0.011) were more commonly linked to ESBL *K. pneumoniae* BSIs (Table 4).

Risk Factors for Poor Prognosis in Neonates with *Escherichia coli* and *Klebsiella pneumoniae* Bloodstream Infections

The results of the univariate and multivariate analysis were depicted in Table 5. The percentages of favorable and poor prognosis in neonates afflicted with bloodstream infections caused by *E. coli* and *K. pneumoniae* stood at 81.29% (113

Table 3 Comparison of Neonatal Variables Between BSIs ESBL-EC and Non-ESBL-EC

Factors	ESBL-EC (29)	Non-ESBL-EC (66)	*P*-value
Basic data			
Gender (male) n(%)	17(58.6)	35(53.0)	0.614
Term infant n(%)	15(51.8)	46(69.7)	0.092
Late premature infant n(%)	10(34.4)	17(25.7)	0.485
Very premature infants n(%)	4(13.8)	3(4.6)	0.112
Normal birth weight n(%)	15(51.8)	44(66.7)	0.167
Low birth weight n(%)	6(20.6)	14(21.2)	0.954
Very low birth weight n(%)	5(17.2)	4(6.1)	0.087
Extremely low birth weight n(%)	3(10.3)	3(4.6)	0.285
Early-Onset infection n(%)	15(51.8)	30(45.4)	0.573
Cesarean section n(%)	14(48.2)	17(25.7)	**0.031**
Premature rupture of membrane n(%)	17(58.6)	28(42.4)	0.145
Breast-fed n(%)	19(65.5)	50(75.7)	0.303
Underlying diseases			
Pneumonia n(%)	9(31.0)	7(10.6)	**0.014**
Enteritis n(%)	0(0.0)	4(6.0)	0.176
Neonatal meningitis n(%)	2(6.8)	5(7.5)	0.907
Hypoalbuminemia n(%)	7(24.1)	15(22.7)	0.881
Anemia n(%)	2(6.8)	12(18.1)	0.153
Invasive procedures and devices			
Mechanical ventilation n(%)	18(62.0)	20(30.3)	**0.004**
Indwelling catheters n(%)	3(10.3)	1(1.5)	**0.048**
Central venous catheterization n(%)	3(10.3)	4(6.0)	0.462
Antibiotic exposure			
Penicillins n(%)	0(0.0)	3(4.5)	0.243
Cephalosporins n(%)	3(10.3)	3(4.5)	0.285
Carbapenem antibiotic n(%)	3(10.3)	4(6.0)	0.462
β-lactam-β-lactamase inhibitors n(%)	4(13.7)	10(15.1)	0.863
Outcomes			
Poor prognosis n(%)	2(6.9)	12(18.2)	0.153
Length of hospital stay (>30 days) n(%)	12(41.4)	8(12.1)	**0.012**

Note: Bold represents $p<0.05$.
Abbreviation: ESBL-EC, extended-spectrum β-lactamase *Escherichia coli*.

Table 4 Comparison of Neonatal Variables Between BSIs ESBL-KP and Non-ESBL-KP

Factors	ESBL-KP (13)	Non-ESBL-KP (21)	*P*-value
Basic data			
Gender (male) n(%)	10(76.9)	9(42.8)	0.051
Term infant n(%)	1(7.7)	8(38.0)	0.051
Late premature infant n(%)	11(84.6)	10(47.6)	**0.031**
Very premature infants n(%)	1(7.7)	3(14.2)	0.562
Normal birth weight n(%)	1(7.7)	8(38.0)	0.051
Low birth weight n(%)	4(30.7)	8(38.0)	0.664
Very low birth weight n(%)	8(61.6)	3(14.2)	**0.004**
Extremely low birth weight n(%)	0(0.00)	2(9.5)	0.251
Early-Onset infection n(%)	1(7.7)	1(4.7)	0.724
Cesarean section n(%)	10(76.9)	9(42.8)	0.052
Premature rupture of membrane n(%)	6(46.1)	7(33.3)	0.455
Breast-fed n(%)	8(61.6)	14(66.6)	0.761

(*Continued*)

Table 4 (Continued).

Factors	ESBL-KP (13)	Non-ESBL-KP (21)	*P*-value
Underlying diseases			
Pneumonia n(%)	3(23.0)	4(19.0)	0.425
Enteritis n(%)	1(7.6)	3(14.20	0.562
Neonatal meningitis n(%)	0(0.00)	1(4.7)	0.425
Hypoalbuminemia n(%)	8(61.6)	11(52.3)	0.601
Anemia n(%)	7(53.8)	12(57.1)	0.851
Invasive procedures and devices			
Mechanical ventilation n(%)	13(100.0)	13(61.9)	**0.011**
Indwelling catheters n(%)	0(0.0)	2(9.5)	0.251
Central venous catheterization n(%)	0(0.0)	2(9.5)	0.251
Antibiotic exposure			
Penicillins n(%)	2(15.3)	1(4.7)	0.289
Cephalosporins n(%)	2(15.3)	3(14.2)	0.93
Carbapenem antibiotic n(%)	1(7.7)	3(14.2)	0.562
β-lactam-β-lactamase inhibitors n(%)	11(84.6)	11(52.3)	0.056
Outcomes			
Poor prognosis n(%)	1(15.4)	3(14.3)	0.929
Length of hospital stay (>30 days) n(%)	9(69.2)	10(47.6)	0.517

Note: Bold represents p<0.05.
Abbreviation: ESBL-KP, extended-spectrum β-lactamase *Klebsiella pneumonia*.

Table 5 Logistic Regression Analysis for Variables Associated with Poor Prognosis of Neonates BSIs with *E. coli* and *K. pneumonia*

Factors	Univariate			Multivariate	
	Poor Prognosis Group (n=26)	Favorable Prognosis Group (n=113)	*P*-value	OR (95% CI)	*P*-value
Basic data					
Gender (male) n(%)	13(50.0)	61(53.9)	0.714		
Term infant n(%)	9(34.6)	61(53.9)	0.075		
Late premature infant n(%)	9(34.6)	47(41.6)	0.513		
Very premature infants n(%)	8(30.8)	5(4.5)	**0.000**	3.763(0.478–29.655)	0.208
Normal birth weight n(%)	9(34.6)	59(52.2)	0.106		
Low birth weight n(%)	3(11.5)	31(27.4)	0.089		
Very low birth weight n(%)	6(23.1)	19(16.8)	0.453		
Extremely low birth weight n(%)	8(30.8)	3(2.6)	**0.000**	4.522(0.490–41.736)	0.183
Early-Onset infection n(%)	9(34.6)	38(33.6)	0.924		
Cesarean section n(%)	9(34.6)	46(40.7)	0.567		
Premature rupture of membrane n(%)	9(34.6)	53(46.9)	0.256		
Breast-fed n(%)	17(65.4)	81(71.6)	0.526		
Underlying diseases					
Pneumonia n(%)	4(15.3)	19(16.8)	0.860		
Enteritis n(%)	2(7.6)	7(6.1)	0.780		
Neonatal meningitis n(%)	3(11.5)	6(5.3)	0.245		
Hypoalbuminemia n(%)	18(69.2)	32(28.3)	**0.000**	3.922(1.189–12.937)	**0.025**
Anemia n(%)	14(53.8)	29(25.6)	**0.015**	0.842(0.229–3.099)	0.796

(*Continued*)

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Table 5 (Continued).

Factors	Univariate			Multivariate	
	Poor Prognosis Group (n=26)	Favorable Prognosis Group (n=113)	*P*-value	OR (95% CI)	*P*-value
Invasive procedures and devices					
Mechanical ventilation n(%)	18(69.2)	56(49.5)	0.070	0.384(0.100–1.473)	0.163
Indwelling catheters n(%)	1(3.8)	6(5.3)	0.758		
Central venous catheterization n(%)	4(15.3)	6(5.3)	0.073	2.328(0.301–18.030)	0.419
Microorganism					
ESBL-EC	2(7.6)	27(23.8)	0.067		
ESBL-KP	2(7.6)	11(9.7)	0.747		
CRKP	7(26.9)	3(2.6)	**0.000**	11.458(1.785–74.708)	**0.010**

Note: Bold represents p<0.05.

Abbreviations: ESBL-KP, extended-spectrum β-lactamase *Klebsiella pneumonia*; ESBL-EC, extended-spectrum β-lactamase *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumonia*; OR, odds ratio; CI, confidence interval.

out of 139) and 18.71% (26 out of 139), respectively. Univariate analysis indicated that very premature infants (p=0.000), extremely low birth weight (p=0.000), hypoalbuminemia (p=0.000), anemia (p=0.015), and isolation of CRKP (p=0.000) were significantly correlated with poor prognosis. In the multivariate analysis, hypoalbuminemia (OR: 3.922, 95% CI: 1.189–12.937, p=0.025), and isolation of CRKP (OR: 11.548, 95% CI: 1.785–74.708, p=0.010) were identified as significant predictors of poor prognosis in neonates afflicted with bloodstream infections caused by *E. coli and K. pneumonia*.

Discussion

Bloodstream infections in newborns caused by *E. coli* and *K. pneumoniae* present a formidable challenge, given the rising prevalence of ESBL and CR strains, especially in healthcare facilities, and they are two of the drivers of nosocomial and community infections globally.[17,18] Between 2017 and 2023, at the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region in Southwest China, we found that approximately one-third of the 139 BSIs caused by *E. coli* and *K. pneumoniae* were due to ESBL strains and 7.2% were due to CRKP. Among these strains, 20.8% were ESBL-EC, whereas only 9.3% were ESBL-KP. This finding was almost similar to the frequencies of ESBL producers among the neonates in the previous two studies, which reported ESBL-EC at 30.4% and ESBL-KP at 8.2%.[19,20] However, a previous study about neonatal sepsis in low- and middle-income countries revealed a much higher prevalence of ESBL-EC (38%) and ESBL-KP (83%) compared to the findings in this study.[21] Furthermore, previous studies conducted in china have reported even higher percentages.[22,23] Consistent findings have been documented in the literature from various regions, such as Iran,[24] South Africa,[25] Ghana,[26] and India.[27] These findings could potentially be attributed to variations in phenotypic detection methods for ESBL production and differences within the study populations.

Genes encoding ESBL are predominantly located on transposons or insertion sequences within plasmids in conjunction with other resistance genes.[8] Consequently, they have the potential to disseminate quickly, leading to resistance against multiple antimicrobials including aminoglycosides, cephalosporins, trimethoprim, sulfonamides, tetracyclines, chloramphenicol, and fluoroquinolones.[28] The antibiotic resistance profiles from our study also showed that ESBL-EC exhibited a higher resistance rate to cephalosporins, fluoroquinolones, tetracyclines compared to non-ESBL strains. Meanwhile, ESBL-KP demonstrated elevated resistance rates to aminoglycosides, β-lactam-β-lactamase inhibitors, cephalosporins, sulfonamides, chloramphenicol, and fluoroquinolones. According to the guidelines from the Infectious Diseases Society of America, carbapenems, fluoroquinolones, and cotrimoxazole are recommended for the treatment of infections outside of the urinary tract caused by ESBL-E.[29] However, high resistance to fluoroquinolones and cotrimoxazole has been found in our study, consistent with prior research.[18] In contrast, no ESBL-E strains exhibited resistance to carbapenems, and ESBL-KP strains showed a resistance rate of 22.7% to imipenem and meropenem, which agrees with earlier studies in Zambia and México.[30,31] Therefore, it is crucial to monitor the resistance profiles of commonly used

antibiotics in the local area. Of utmost importance is the monitoring of the resistance patterns displayed by ESBL isolates and understanding their impact on patient management, particularly among neonates.

The clinical characteristics associated with neonatal BSIs caused by ESBL isolates are vital for the prevention of these infections and the effective administration. Co-morbidities like cesarean section, prematurity, very low birth weight, pulmonary disease, malnutrition, malignancy, gastroenteritis, mechanical ventilation, indwelling catheters, central venous catheterization were investigated as risk factors for neonatal BSIs due to ESBL-E isolates.[32–35] In our study, patients with late premature infant, very low birth weight, cesarean section, pneumonia, and mechanical ventilation also had a higher risk of ESBL isolates bloodstream infection. Furthermore, we conducted a detailed analysis of the risk factors associated with ESBL-EC and ESBL-KP neonatal BSI. Our investigation revealed a distinct correlation between ESBL-EC infections with cesarean section, pneumonia, mechanical ventilation, and indwelling catheters, whereas ESBL-KP infections showed a notably association with the presence of late premature infants, very low birth weight, and mechanical ventilation. This finding indicates that different subtypes of Enterobacteriaceae bacteria carrying ESBL may demonstrate variations in their pathogenicity and impact on host resistance. *E. coli* and *K. pneumoniae* are the most prevalent hosts of ESBL.[8] The ST131 clone is predominant in ESBL-producing *E. coli*, while ST11 is dominant in ESBL-producing *K. pneumoniae*.[11,36] These strains harbor distinctive biological traits or pathogenic mechanisms that enhance their propensity to serve as risk factors for bloodstream infections. Nevertheless, studies on the virulence and molecular epidemiological characteristics have not been undertaken. Subsequent research should prioritize whole-genome sequencing and functional assessments to elucidate the molecular mechanisms that underlie these adaptations and pathogenicity, thereby informing targeted interventions.

Although we have conducted a statistical analysis on the risk factors associated with ESBL strains infections, the total number of ESBL infection cases is insufficient for a multivariate analysis. Consequently, we undertook a study analyzing the prognosis of 139 cases of neonatal bloodstream infections to identify the risk factors contributing to poor prognosis. Our study indicated that very premature infants, extremely low birth weight, hypoalbuminemia, anemia, and isolation of CRKP were significantly correlated with a poor prognosis. In the management of neonates, invasive procedures and devices such as mechanical ventilation and central venous catheterization, although crucial for life support, heighten the vulnerability to infections in newborns, especially premature infants and those with low birth weight.[37] Research has confirmed that prematurity, low birth weight, hypoalbuminemia, anemia, CRKP, and invasive procedures such as mechanical ventilation are associated with a poor prognosis for neonatal BSI.[38–41] Consistent with our research results, further studies are needed to explore the specific mechanisms. Importantly, isolation of CRKP and hypoalbuminemia were identified as significant predictors of poor prognosis in neonates afflicted with bloodstream infections caused by *E. coli* and *K. pneumonia*. In line with the findings of Dilan et al[39] and Yasemin et al[42] recent research has consistently demonstrated that the presence of carbapenem-resistant gram-negative bacteria, specifically isolation of CRKP serves as a significant predictor of unfavorable outcomes in neonatal bloodstream infections. According to the results of our search in the PubMed database, we did not retrieve any relevant literature indicating that hypoalbuminemia is an independent risk factor for poor prognosis in neonatal BSI. Proteins play vital roles in the body, contributing to immune function, nutrient metabolism, and cell structure. Newborns have an immature immune system at birth, and hypoalbuminemia could potentially compromise immune function, elevating the susceptibility to infections. In the context of neonatal BSI, hypoalbuminemia might worsen the disease severity, impacting treatment efficacy and prognosis.

Our study was subject to certain limitations. The predominant limitation pertained to its retrospective study and single-center design, encompassing a cohort of 139 neonatal patients, thereby rendering it susceptible to selection bias. Further prospective, multicenter studies are warranted. Secondly, our research exclusively targeted bloodstream infections caused by *E. coli* and *K. pneumoniae*, without encompassing other gram-negative bacteria. Furthermore, our research has focused solely on drug resistance phenotypes rather than delving into the molecular aspects such as drug resistance mechanisms, virulence, and molecular epidemiology studies. Exploring the correlation between strain molecular characteristics and clinical traits is crucial for infection prevention and control, which will be the primary focus of our future investigations. Lastly, the study design did not include a preset long-term follow-up, resulting in a lack of data on mortality within 28 days, which limits the completeness of the research conclusions and the evaluation of long-term patient outcomes. In future studies, we will consider incorporating a long-term follow-up plan to more comprehensively assess treatment efficacy and patient prognosis.

Conclusion

The predominant children's hospital in this autonomous region exhibits a relatively low incidence of ESBL-EC and ESBL-KP. Compared to non-ESBL strains, ESBL strains demonstrated a higher resistance rate to cephalosporins, fluoroquinolones, and tetracyclines. Late-preterm infants, very low birth weight, cesarean section history, pneumonia, and mechanical ventilation were found to be associated with bloodstream infections caused by ESBL strains. The isolation of CRKP and hypoalbuminemia were identified as significant predictors of poor prognosis in neonates afflicted with bloodstream infections caused by *E. coli* and *K. pneumonia*. The implementation of infection control initiatives and antimicrobial stewardship programs is critical for controlling healthcare expenditures, reducing antimicrobial resistance rates, enhancing patient outcomes, and mitigating the adverse ecological impacts of antimicrobial overuse.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This research adhered to the ethical principles outlined in the Declaration of Helsinki and followed applicable guidelines. Ethical approval was obtained from the Institutional Review Board of the Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region (Approval No. 2023-3-42). Since the study involved a retrospective analysis of de-identified medical records, participant privacy was safeguarded, and no additional risks were introduced. Due to the use of anonymized data and the study's retrospective design, the ethics committee granted an exemption from obtaining informed consent.

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Author Contributions

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

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Disclosure

The authors declare that they have no conflict of interest.

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