Original Research Article

Differences in clinical characteristics of early- and late-onset neonatal sepsis caused by *Klebsiella* pneumoniae

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Abstract

To identify differences in the clinical characteristics of early- and late-onset sepsis (EOS and LOS) caused by *Klebsiella pneumoniae* (*K. pneumoniae*) and to describe the risk factors for multidrug-resistant *K. pneumoniae* (MDR-KP) infection. Infants with *K. pneumoniae*-induced sepsis who were admitted to a children's Hospital between Jan 2000 and Dec 2019 were included. All infants were divided into EOS and LOS groups, as well as MDR-KP and non-MDR-KP groups. Demographics, clinical characteristics, and risk factors were compared between the two groups. One hundred eighty infants (66 with EOS and 114 with LOS) were further analyzed, accounting for 36.8% of sepsis cases caused by MDR-KP. The frequency of respiratory failure, bronchopulmonary dysplasia, and intraventricular hemorrhage were more common in the LOS group and a higher rate of acute respiratory distress syndrome was more common in infants in the EOS group ($P < 0.05$). *K. pneumoniae* showed a low sensitivity to penicillin, beta-lactams and cephalosporins, and it showed a high sensitivity to levofloxacin, ciprofloxacin, and amikacin. Prematurity, low birth weight, longer antibiotic exposure time, long duration of peripheral catheter insertion, long mechanical ventilation time, and long parenteral nutrition time were associated with an increased rate of MDR-KP infection by univariate analysis ($P < 0.05$). The regression analysis identified a long antibiotic exposure time (OR = 1.37, 95% CI: 1.01–1.89) and long parenteral nutrition time (OR = 1.39, 95% CI: 1.01–1.89) as independent risk factors for a MDR-KP infection, and a greater gestational age and birth weight were associated with a lower risk of MDR-KP infection (OR = 0.57, 95% CI: 0.40–0.79). LOS caused by *K. pneumoniae* may lead to a higher frequency of complications. The risk factors for MDR-KP infection were longer duration of antibiotic exposure and parenteral nutrition. A greater gestational age and larger birth weight may decrease the risk of MDR-KP infection.

Keywords

antibiogram, early-onset sepsis, *Klebsiella pneumoniae*, late-onset sepsis, multidrug-resistant, neonate

Introduction

Neonatal sepsis remains a major cause of neonatal morbidity and mortality, particularly in preterm newborns and newborns with a very low birth weight (VLBW).[1–3] In the USA, the incidence of neonatal sepsis ranges from one to four infections per 1000 livebirths.[4] In four Asian centers (mainland China, Thailand, Macau, and Malaysia), the overall

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incidence of neonatal sepsis was 26.1 per 1000 admissions.[4] Neonatal sepsis is one of the most common causes of neonatal death, killing 0.421 million neonates worldwide in 2013.[5] According to Laxminarayan,[6] 214,000 of 690,000 annual neonatal deaths (31%) are associated with sepsis.

Neonatal sepsis is divided into early-onset (defined as the onset of sepsis in the first three days of life) and late-onset (after day three of life) sepsis.[1] Early-onset sepsis (EOS) is associated with prematurity, a low birth weight, and obstetric complications, such as premature rupture of membranes (PROM), and chorioamnionitis,[7–10] and the major gram-negative pathogen causing EOS is *Escherichia coli*.[8–10] In contrast, late-onset sepsis (LOS) is related to prematurity, a low birth weight, invasive procedures such as resuscitation in the delivery room, tracheal intubation, mechanical ventilation, central venous catheter placement, and surgical procedures.[11,12] Pathogens causing LOS vary worldwide, and reports more commonly show that the causative agent is gram-positive organisms,[13] while gram-negative organisms in infants with LOS requiring tracheal intubation and mechanical ventilation have also been reported.[11–13] EOS and LOS have their own characteristics in terms of risk factors and clinical features.[12,14,15]

Klebsiella pneumoniae (*K. pneumoniae*) is a common and important pathogen causing neonatal infections, and multidrug-resistant *K .pneumoniae* (MDR-KP) in particular poses an urgent threat to public health.[16,17] Notably, *K. pneumoniae* resistance varies considerably between countries, as MDR-KP is endemic to eastern and southwestern Europe, as well as Mediterranean countries, and the rates of resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides exceed 50%–60%.[16,17] Regarding carbapenems, almost all regions were previously free of carbapenem-resistant *K. pneumoniae*, but carbapenem-resistant *K. pneumoniae* emerged in 2015 in several countries, including Romania, Italy, and Greece, reaching resistance rates of 40%–60%.[17,18–20] In China, the overall prevalence of imipenem-resistant *K. pneumoniae* increased from 3.0% to 20.9% and the prevalence of meropenem-resistant *K. pneumoniae* increased from 2.9% to 24.0% between 2005 and 2017.[21]

To our knowledge, few studies have reported EOS caused by *K. pneumoniae*, and LOS caused by *K. pneumoniae* has also been only simply been mentioned[2,22]; therefore, the difference in EOS and LOS due to *K. pneumoniae* infection remains unclear. In addition, limited recent data are available on neonate sepsis caused by MRD-KP. This study had two aims. First, we compared the differences in the clinical features and drug sensitivity of neonates with sepsis caused by *K. pneumoniae*. Second, we identified the epidemiology and clinical features of infants with sepsis due to an MDR-KP infection compared with infants with sepsis caused by a non-MDR-KP infection and to identify risk factors for MDR-KP infection.

Materials and methods

Study population

This retrospective study was conducted at the Neonatal Diagnosis and Treatment Center of the Children's Hospital of Chongqing Medical University (CHCMU) between Jan 2000 and Dec 2019. Neonates with *K. pneumoniae*-induced sepsis were grouped into an early-onset group (symptom onset within 3 days after birth) and a late-onset group (symptom onset after 3 days of life).[1] The definition of *K. pneumoniae*-induced sepsis was a positive blood or cerebrospinal fluid culture with clinical manifestations of sepsis, consistent with the diagnostic criteria for neonatal sepsis.[23] MDR-KP was defined according to the international expert proposal of European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.[24] Acute respiratory distress syndrome (ARDS) was diagnosed according to the Montreux definition of neonatal ARDS.[25] Hypoglycemia was defined as a blood glucose level <47 mg/dL (2.61 mmol/L).[26] Bronchopulmonary dysplasia (BPD) was defined as a requirement for supplemental oxygen or positive pressure support at 36 weeks of postmenstrual age, with severe BPD defined according to the National Institutes of Health criteria.[27] The diagnostic criteria for intraventricular hemorrhage (IVH) were graded according to the Papile criteria.[28] Infants lacking infectious clinical manifestations were excluded from further study, despite the presence of a positive blood culture.

Data collection

Medical charts were reviewed, and the gestational age, birth weight, sex, age of infection, age at admission and other medical parameters were extracted. Maternal and prenatal data were collected, including maternal chronic diseases, gestational diabetes mellitus, maternal hypertension, intrahepatic cholestasis

of pregnancy, PROM >18h, antenatal steroid exposure, chorioamnionitis and clinical complications. The laboratory test results, drug sensitivity of *K. pneumoniae*, presence of a peripherally inserted central catheter (PICC), parenteral nutritional status, antibiotic therapeutic strategy, pulmonary surfactant (PS) therapy, respiratory support, and prognosis were also collected. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University (No: 2016-16), and use of the database housing the evaluated data was permitted by the ethics committees of CHCMU. The data were collected, reviewed, identified, and anonymously analyzed by the authors, and the Ethics Committee waived the requirement for informed consent due to the anonymized nature of the data and scientific purpose of the study.

Statistical analysis

All analyses were performed using SPSS statistical software (version 17, SPSS, Chicago, IL, USA). Data are presented as means ($\pm$ S.D.), or as medians and interquartile ranges (IQRs), and Student's test or the Mann–Whitney U test was used to analyze the significance of differences in continuous variables as necessary. The chi-squared or Fisher exact test was used to analyze the significance of differences in categorical variables. Relationships between continuous variables were analyzed by calculating Pearson's correlation coefficients. When analyzing the risk factors for MDR-KP infection, logistic regression analyses were performed to determine significant independent associations of demographic variables, such as gestational age, birth weight, time of antibiotic exposure, PICC, mechanical ventilation and parenteral nutrition before diagnosis, and the MDR-KP infection. Before performing the logistic regression analysis, the collinearity between multiple continuous variables was tested; if collinearity was identified, collinear variables were subjected to a principal component analysis, and a subsequent logistic regression analysis was conducted to identify the independent risk factor. $P < 0.05$ was considered statistically significant.

Results

Baseline information

During the study period, 111,996 infants were admitted to the CHCMU. Among them, 4785 suffered from sepsis and blood cultures positive for

K. pneumoniae were obtained from 201 infants, but 21 of these infants were excluded from the present study because of blood sample contamination. Therefore, 180 infants met the inclusion criteria. Among those infants, 66 (36.7%) suffered from EOS and 114 (63.3%) from LOS, 66 (36.7%) had sepsis caused by MDR-KP, 105 (58.3%) were male, 91 (50.6%) were preterm, and 110 (61.1%) were infants with a LBW. PROM and chorioamnionitis were identified in 41 and 17 infants, respectively. PS and antenatal steroids were administered to 40 and 56 infants, respectively.

Clinical features of EOS and LOS

Table 1 shows the overall demographic characteristics of infants with EOS and LOS. Higher rates of a lower gestational age, lower birth weight, early age of infection, and early age at admission were observed among infants with LOS than infants with EOS ($P < 0.05$).

Table 2 provides a summary of the clinical characteristics associated with EOS and LOS. Compared with infants with EOS, infants with LOS showed higher frequencies of respiratory failure, BPD, and IVH ($P < 0.05$). Meanwhile, a higher rate of acute respiratory distress syndrome (ARDS) was observed in infants in the EOS group ($P < 0.05$). The occurrence of other clinical complications, including septic shock, purulent meningitis, pulmonary hemorrhage, necrotizing enterocolitis (NEC), hypoglycemia, and renal insufficiency, was not significantly different between the two groups ($P > 0.05$).

Table 3 lists the drug resistance rates of *K. pneumoniae* to commonly used antimicrobials. In both groups, *K. pneumoniae* showed a low sensitivity to penicillin (1.2%–10.3%), beta-lactams (18.8%–39.1%) and cephalosporins (12.8%–28.5%), and a high sensitivity to quinolones (86.0%–92.2%) and aminoglycosides (71.5%–96.0%). Notably, 43.3% of *K. pneumoniae* isolates produced Extended-Spectrum β-Lactamases (ESBL) and 39.3% of *K. pne*umoniae isolates were resistant to carbapenem. No significant difference was observed in the drug resistance rates between the EOS and LOS groups ($P < 0.05$).

Features of MDR-KP sepsis and risk factors for MDR-KP infection

Table 4 shows the overall demographic characteristics of infants with sepsis caused by MDR-KP

Table 1. Demographic characteristics of infants enrolled in the present study.

Variable	EOS (N = 66)	LOS (N = 114)	$\chi^2/Z/t$	P
	% (n), M (P$_{25}$–P$_{75}$), mean $\pm$ S.D			
Male/female	38/28	67/47	0.025	0.875
Gestational age, w	37.0 (33.0–39.3)	31.6 (29.0–38.0)	4.642	0.000
Birth weight, g	2590 (1623–3185)	1410 (1173–3000)	3.766	0.000
Age at admission, d	4.77 (0.19–8.49)	0.19 (0.48–10.63)	2.485	0.013
Age at infection, d	1.3 (0.6–2.4)	21.5 (12.8–34.0)	10.493	0.000
Prematurity	33.3 (22)	60.5 (69)	12.365	0.000
Low birth weigh	47.0 (31)	69.3 (79)	8.769	0.003
Chorioamnionitis	7.6 (5)	10.5 (12)	0.425	0.514
premature rupture of membranes (>18h)	25.8 (17)	21.1 (24)	0.526	0.468
Maternal hypertension	7.6 (5)	9.6 (11)	0.222	0.638
Gestational diabetes mellitus	13.6 (9)	21.9 (25)	1.877	0.171
Meconium stained amniotic fluid	7.6 (5)	10.5 (12)	0.425	0.514
Antenatal steroid use	24.2 (16)	35.1 (40)	2.294	0.130
Cesarean section	59.1 (39)	54.4 (62)	0.376	0.540
Pulmonary surfactant use	15.2 (10)	26.3 (30)	3.014	0.083
Hospitalization duration, d	24.5 $\pm$ 20.96	46.27 $\pm$ 26.9	5.651	0.000
Mortality	28.2 (19)	16.7 (19)	3.688	0.055

Table 2. Comparison of neonatal complications between the two groups of infants. (% (n)).

Variable	EOS (N = 66)	LOS (N = 114)	χ^2	P
Respiratory failure	36.4 (24)	53.5 (61)	4.930	0.026
persistent pulmonary hypertension of newborn	13.6 (9)	15.8 (18)	0.152	0.697
Acute respiratory distress syndrome	19.7 (13)	6.1 (7)	7.778	0.005
Bronchopulmonary dysplasia	4.5 (3)	18.4 (21)	6.964	0.008
Intraventricular hemorrhage	21.2 (14)	39.5 (45)	6.326	0.012
Septic shock	1.5 (1)	10.5 (12)	3.810	0.051
Pulmonary hemorrhage	6.1 (4)	15.8 (18)	3.688	0.055
Necrotizing enterocolitis	18.2 (12)	17.5 (20)	0.012	0.914
Hypoglycemia	21.2 (14)	21.9 (25)	0.013	0.910
Coagulation disorders	57.6 (38)	52.6 (60)	0.412	0.521
Purulent meningitis	21.2 (14)	20.2 (23)	0.028	0.868
Renal insufficiency	21.2 (14)	26.3 (30)	0.590	0.443

and non-MDR-KP infections. All MDR-KP infections were identified in the LOS group, and a lower gestational age, lower birth weight, longer time of antibiotic exposure, PICC, mechanical ventilation, and parenteral nutrition before diagnosis were more common in the MDR-KP infection group ($P < 0.05$). The age at infection in the MDR-KP group was older compared with the non-MDR-KP infection group ($P < 0.05$). Meanwhile, the age at admission was earlier and a greater requirement for PS therapy was observed in infants in the MDR-KP infection group ($P < 0.05$). No differences in maternal factors, neonatal gender, and pattern of delivery were observed ($P > 0.05$). Furthermore, the age at infection in the MDR-KP infection group was inversely correlated with the gestational age and birth weight (Figures 1A and 1B).

Table 5 shows the independent risk factors for MDR-KP infection. Before conducting the logistic regression analysis, continuous variables, including gestational age, birth weight, duration of antibiotic exposure, PICC, mechanical ventilation, and parenteral nutrition before diagnosis, were subjected to a collinearity analysis. Collinearity existed between the following variables: (1) gestational age and birth weight, which were further defined as the congenital nutritional factor; (2) PICC time and parenteral nutrition time, which were further defined as the postnatal parenteral nutritional support factor. The logistic regression analysis was subsequently

Table 3. Rates of *K. pneumoniae* susceptibility to different antibiotics (% (n/N)).

Variable	Total (N = 180)	EOS (N = 66)	LOS (N = 114)	χ^2	P
Penicillin					
Ampicillin	1.2 (2/167)	0.0 (0/63)	1.9 (2/104)	–	0.527
Piperacillin	10.3 (16/155)	13.3 (8/60)	8.4 (8/95)	0.959	0.328
Beta-lactam					
Ampicillin plus sulbactam	18.8 (33/176)	24.2 (16/66)	15.5 (17/110)	2.091	0.148
Piperacillin plus tazobactam	39.1 (70/179)	54.5 (36/66)	30.1 (34/113)	10.465	0.001
Cephalosporin					
Cefazolin	12.8 (22/172)	14.3 (9/63)	11.9 (13/109)	0.199	0.655
Ceftazidime	28.5 (51/179)	39.4 (26/66)	22.1 (25/113)	6.099	0.014
Cefotaxime	17.4 (31/178)	19.7 (13/66)	16.1 (18/112)	0.380	0.538
Carbapenem					
Imipenem	60.7 (105/173)	90.8 (59/65)	42.6 (46/108)	39.478	0.000
Quinolone					
Levofloxacin	92.2 (165/179)	98.5 (65/66)	88.5 (100/113)	5.767	0.016
Ciprofloxacin	86.0 (154/179)	95.5 (63/66)	80.5 (91/113)	7.723	0.005
Aminoglycoside					
Amikacin	96.0 (169/176)	100.0 (66/66)	93.6 (103/110)	2.866	0.090
Gentamicin	71.5 (128/179)	71.2 (47/66)	71.7 (81/113)	0.005	0.946
Others					
MDR-KP, % (n)	36.7 (66/180)	0.0 (0/66)	57.9 (66/114)	60.332	0.000
ESBL, % (n)	43.3 (78/180)	65.2 (43/66)	30.7 (35/115)	20.202	0.000

ESBL: Extended-Spectrum β-Lactamases; MDR-KP: multidrug-resistant *K. pneumoniae*.

Table 4. Demographic characteristics and risk factors of infants in the two groups.

Variable	Non-MDR-KP (N = 114)	MDR-KP (N = 66)	χ^2/Z/t	P
	% (n), M (P$_{25}$–P$_{75}$), mean ± S.D			
Maternal factors				
Chorioamnionitis	7.0 (8)	13.6 (9)	2.141	0.143
Antenatal steroid use	27.2 (31)	37.9 (25)	2.227	0.136
Maternal hypertension	8.8 (10)	9.1 (6)	0.005	0.942
Premature rupture of membranes (>18h)	25.4 (29)	18.2 (12)	1.251	0.263
Meconium stained amniotic fluid	8.8 (10)	10.6 (7)	0.164	0.685
Gestational diabetes mellitus	27.3 (18)	14.0 (16)	4.781	0.029
Neonatal factors				
Male	61.4 (70)	53.0 (35)	1.206	0.272
Gestational age, w	36.7 (31.3–39.1)	30.3 (28.1–35.4)	4.467	0.000
Prematurity	41.2 (47)	66.7 (44)	10.821	0.001
Birth weight, g	2450 (1405–3205)	1340 (1150–2280)	3.986	0.000
Low birth weight	52.7 (58)	47.3 (52)	13.702	0.000
twin	12.1 (8)	16.7 (19)	0.677	0.41
Cesarean section	57.9 (66)	53.0 (35)	0.402	0.526
Age of infection, d	3.0 (1.0–21.0)	20.5 (11.8–32.3)	5.297	0.000
Age at admission, d	5.14 (0.11–11.89)	0.08 (0.04–2.20)	4.702	0.000
Late onset sepsis	42.1 (48)	100 (66)	60.332	0.000
Duration of antibiotic exposure before diagnosis, d	1.0 (0.0–14.3)	12.0 (6.8–21.0)	4.804	0.000
Antibiotic exposure before diagnosis	55.3 (63)	90.9 (60)	24.545	0.000
PICC time before diagnosis, d	0.0 (0.0–11.0)	14.0 (7.5–23.0)	5.521	0.000
PICC time before diagnosis	31.6 (36)	83.3 (55)	44.790	0.000
Duration of mechanical ventilation, d	0.0 (0.0–0.0)	0.0 (0.0–4.0)	2.810	0.005
Mechanical ventilation before diagnosis	21.1 (24)	39.4 (26)	7.009	0.008
Duration of parenteral nutrition before diagnosis, d	0.0 (0.0–21.0)	20.0 (9.0–31.0)	5.250	0.000
Pulmonary surfactant use	14.0 (16)	36.4 (24)	12.057	0.000
Hospitalization duration, d	31.56 ± 24.86	49.92 ± 26.64	4.651	0.000
Mortality	21.2 (24)	21.2 (14)	0.001	0.98

PICC: peripherally inserted central catheter.
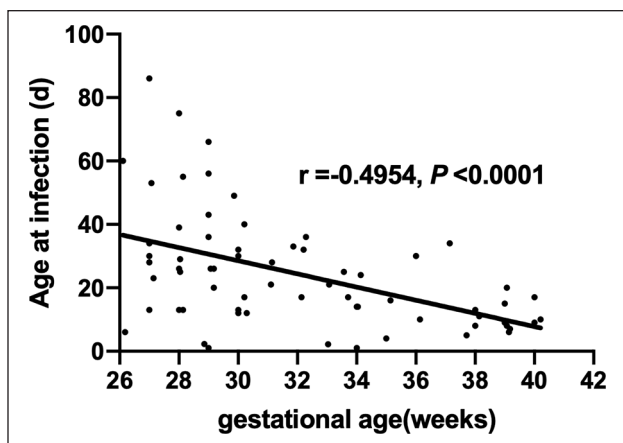
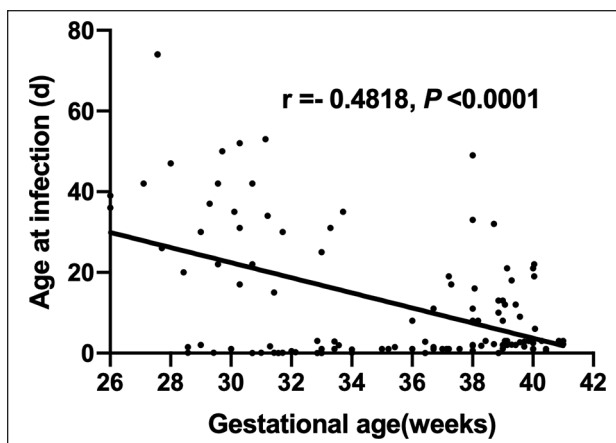**Figure 1A.** The relationship between the age at which the MDR-KP infection was acquired and gestational age.

Figure 1B. The relationship between the age at which the MDR-KP infection was acquired and birth weight.

performed (Table 5). The congenital nutritional factor was identified as a protective factor, suggesting that a higher gestational age and birth weight resulted in a lower risk of MDR-KP infection. The postnatal parenteral nutritional support factor was considered a risk factor, suggesting that a longer time of parenteral nutrition and PICC resulted in a greater risk of MDR-KP infection. Meanwhile, a longer duration of antibiotic exposure would increase the risk of MDR-KP infection. The associations between the temporal distribution of MDR-KP infection and the independent risk factors are shown in Figure 2.

Treatment and prognosis

All infants were treated with antibiotics according to the drug sensitivity reports. Other treatment protocols, including total parental nutrition and intensive care (cardiorespiratory support, blood or blood products transfusion), were administered when necessary. Although no difference in mortality was observed between the EOS and LOS groups, the duration of hospitalization was much longer in infants in the EOS group than in the LOS group (Table 1). Meanwhile, the mortality in the MDR-KP infection group was similar to the Non-MDR-KP infection group; however, the duration of hospitalization was longer in infants in the MDR-KP infection group (Table 4). Sixteen of the 20 infants with ARDS were treated with PS, and no significant difference in mortality was observed between the infants treated with PS and without PS (25% (4/16) vs 25% (1/4), $\chi^2 = 0.000$, $P = 1.0$).

Discussion

A previous study identified preterm birth/low birth weight as the risk factors most closely associated with EOS.[29] Meanwhile, preterm birth/low birth weight are also risk factors for LOS.[13] In the present investigation, a greater percentage of infants with a lower birth weight and gestational age had LOS. This finding might be related to prematurity, and low birth weight infants have a more immature immune system, which requires longer periods of parenteral nutrition and hospitalizations, coupled with invasive procedures such as intravenous catheterization and mechanical ventilation, placing them at higher risk for LOS.[30]

Neonatal sepsis might be complicated with purulent meningitis, septic shock, disseminated intravascular coagulation and other life-threatening conditions. In the present study, we also observed a higher rate of complication with ARDS in infants with EOS caused by *K. pneumoniae* infection. ARDS usually develops due to a secondary deficiency of PS caused by a variety of inflammatory processes.[31] Sepsis generally initiates a systemic inflammatory response, and proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin 1 beta (IL-1β), IL-6, and IL-8,[32,33] are released. These cytokines activate neutrophils to produce toxic mediators and damage the endothelium and alveolar epithelium,[34–36] eventually leading to alveolar–capillary barrier injury.[30,37] Then, the protein-rich fluid induces acute pulmonary edema and inactivates PS.[36] In addition, the inflammatory reaction damages alveolar type II cells and decreases the quantity of PS synthesized;

Table 5. Independent risk factors for MDR-KP infection.

Variables	β	S.E.	Wald	P	OR (95% CI)
Congenital nutritional factors	−0.57	0.17	10.883	0.001	0.57 (0.40–0.79)
Postnatal nutritional factor	0.33	0.16	4.435	0.035	1.39 (1.02–1.90)
Duration of antibiotic exposure	0.32	0.16	4.175	0.041	1.38 (1.01–1.89)
Constant	−0.61	0.17	13.463	<0.001	–
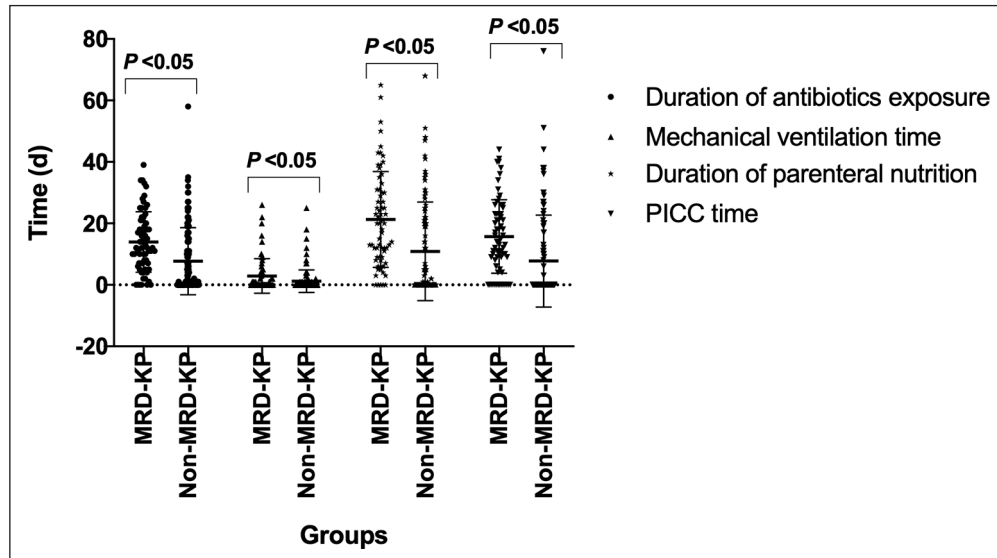
Figure 2. The association between temporal distribution of the MDR-KP infection and independent risk factors.

furthermore, oxidation and hydrolysis activated by the inflammatory reaction increase the degradation of PS.[38] Therefore, PS therapy might not improve the prognosis in those infants with ARDS due to bacterial infection.

In the present study, higher incidence of BPD was observed in infants with LOS, who also had higher percentages of lower gestational age and birth weight. After a bacterial infection, a series of inflammatory responses occur through the release of several cytokines, such as interleukin IL-1, IL-8, and tumor necrosis factor alpha (TNF-α), which may inhibit alveolarization and normal vascular development, compromising the ability of the lungs to heal and causing persistent immune dysregulation.[39] Additionally, LOS induces a proinflammatory and profibrotic response in the preterm lung, predisposing it to BPD.[40] Moreover, premature and low birth weight infants presenting with immature lungs are exposed to ongoing oxidative and invasive procedures, such as mechanical ventilation, which can aggravate lung damage.[41] Based on our findings, clinicians should closely monitor neonates with *K. pneumoniae*-induced sepsis, particularly infants with LOS, for BPD.

In the present study, a higher incidence of IVH was observed in the LOS group with *K. pneumoniae*-induced sepsis than in the EOS group ($P <$ 0.05), potentially because the inflammatory response exerts a direct neurotoxic effect, leads to circulatory disturbances, and induces the adhesion of leukocytes to fragile vessels, all of which may increase the risk of IVH.[42] In addition, in our study, a higher frequency of premature and lower birth weight infants was observed, which are also considered risk factors for IVH.

In the current study, among 180 infants with sepsis, MDR-KP infections were identified in 66 infants, all of whom were in the LOS group. According to the univariate analysis, a low gestation age, low birth weight, long duration of antibiotic exposure, long PICC time, long mechanical ventilation time and long duration of parenteral nutrition support were risk factors for infection with MDR bacteria. Further logistic regression analyses identified a long duration of antibiotic exposure and parenteral nutrition as independent risk factors for MDR-KP infection, and a greater gestational age and larger birth weight may decrease the risk of MDR-KP infection. Premature and low birth weight infants are susceptible to

infections due to malnutrition, immaturity, a weak immune system, and a poor ability to adapt to the external environment, which are conducive to the growth of pathogenic bacteria.[43] Premature or low birth weight infants often require more invasive procedures, longer parenteral nutrition and a longer duration of hospitalization, and thus they are more likely to develop nosocomial infections, particularly infections with MDR organisms.[44] Invasive operations such as PICC and mechanical ventilation can damage the body's natural barrier, leading to internal and external communication that destroys the patient's own barrier and circulatory pathway,[45] which will undoubtedly decrease immunity and increase the probability of bacterial colonization or infection.[46] Long-term use of antibiotics has been shown to increase the number of drug-resistant strains, producing multidrug-resistant bacteria and even pan-drug resistant strains.[47]

In the present study, *K. pneumoniae* isolates were not susceptible to commonly used antibiotics, such as penicillin, beta-lactams, and cephalosporins. A national surveillance study from the UK showed that 94% of isolates in newborns were sensitive to penicillin + gentamicin, 98% to amoxicillin + penicillin and 96% to monotherapy with cefotaxime.[48] This large difference may be mainly attributed to the abuse of broad-spectrum antibiotics, particularly third-generation cephalosporins in neonates,[49] and intrapartum antibiotic prophylaxis has been linked to the growth of resistant bacteria, mainly bacteria resistant to ampicillin.[50] Furthermore, we observed 43.5% of *K. pneumoniae* produce an ESBL and 39.4% of organisms showed resistance to imipenem in this study. This finding may be related to the significant increase in antibiotic consumption in China and other developing countries, both as prescriptions for patients and feed additives in the agriculture industry. The routine feeding of antibiotics to healthy farm animals, which occurs without a prescription, promotes the development of antibiotic-resistant bacteria that can be transferred to humans.[51] Although a high percentage of *K. pneumoniae* is sensitive to quinolones and aminoglycosides antibiotics, these antibiotics may exert severe side effects on the liver, kidney, hearing, and cartilage development, which make them an inappropriate choice for infants.[52]

Limitations to our study include the errors and bias inherent to retrospective studies. Additionally, some patients were transferred to our center from other hospitals, and data regarding the details of maternal and infant treatment protocols performed outside of our hospital (e.g. the data on the intake of antibiotics by mothers) were limited. Furthermore, in this retrospective study, although we did not calculate the sample size and collected all the clinical data from infants with sepsis, our single-center study may not completely represent drug sensitivity in China, and multicenter studies are recommended in the future.

Conclusion

LOS caused by *K. pneumoniae* was linked to higher complication rates, and *K. pneumoniae* showed a low sensitivity to penicillin, beta-lactams, and cephalosporins and a high sensitivity to levofloxacin, ciprofloxacin, and amikacin. The risk factors for MDR-KP were a long duration of antibiotic exposure, long PICC time and long duration of parenteral nutrition. A reduction in the use of unnecessary invasive procedures might decrease the incidence of MDR-KP infection.

Availability of data and materials

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of the Children's Hospital of Chongqing Medical University (APPROVAL NUMBER/ID:2016-16).

Informed consent

Informed consent was not sought for the present study because it is a retrospective clinical study.

Trial registration

Not applicable.

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