Pathogen Distribution and Antimicrobial Resistance of Early Onset Sepsis in Very Premature Infants: A Real-World Study

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ABSTRACT

Introduction: Early onset sepsis (EOS) remains a potentially fatal newborn condition, especially in very preterm infants. Data on the pathogen distribution and antibiotic susceptibility patterns of EOS among very preterm infants are scarce but essential for the choice of empirical antibiotic administration. We sought to assess the epidemiologic characteristics and
antibiotic susceptibility patterns of pathogens causing EOS among a cohort of very preterm infants in China.

**Methods:** This prospective, observational study included a cohort of infants born at a gestational age (GA) less than 32 weeks of 32 newborn intensive care units (NICUs) in China between January 1, 2018 and December 31, 2020. EOS was defined by isolation of pathogenic species from blood culture within 72 h of birth.

**Results:** A total of 108 EOS cases (18.4 per 1000 admissions) were identified among 5865 very preterm infants. Incidence of EOS increased with the decrease of GA and birthweight. *Escherichia coli* (*n* = 44, 40.7%) was the most common pathogen, followed by *Klebsiella* spp. (*n* = 10, 9.3%). The distribution and proportion of pathogenic bacteria varied significantly by GA. *E. coli* and *Klebsiella* spp. showed high resistance to ampicillin and third-generation cephalosporins, while they showed good susceptibility to carbapenem antibiotics and piperacillin–tazobactam.

**Conclusion:** Our data demonstrated that pathogens causing neonatal EOS showed high rates of resistance to ampicillin and third-generation cephalosporins. This raised questions about the best empirical antibiotic choice for preterm infants suspected of having EOS in low- and middle-income countries (LMICs).

**Keywords:** Infants; Premature; Early-onset neonatal sepsis; Pathogen; Antimicrobial resistance

**Key Summary Points**

- Very preterm infants are at much greater risk for early-onset sepsis (EOS) than more mature infants.
- *E. coli* and *Klebsiella* spp. were the predominant organisms, and both showed high resistance rates to ampicillin and third-generation cephalosporins.
- Empiric treatment should be based on regional EOS pathogen distribution and resistance rates.
- This study highlights the need for improved EOS treatment guidance in LMICs.
INTRODUCTION

Neonatal sepsis is a major cause of morbidity and mortality and is a global health concern, especially in very preterm infant [1, 2]. Neonatal sepsis is a systemic infection and can be classified into two subgroups, early onset sepsis (EOS) and late-onset sepsis (LOS). EOS is most consistently defined as an infection occurring within 72 h after birth caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery [3, 4]. Very preterm infants (gestational age less than 32 weeks) are at high risk of developing EOS, because of their compromised immunity. Survivors of EOS are at increased risk for adverse neurodevelopmental outcomes including cerebral palsy, hearing loss, visual impairment, and cognitive delays [5]. The high incidence and the alarming complications of EOS underscore the need to understand the epidemiological characteristics of EOS in very preterm infants [6].

Accurately diagnosing EOS among very premature infants is challenging because of non-specific clinical symptoms and the difficulty of evaluating infection markers for EOS in the early stage. Antibiotics are initiated in the majority of very preterm infants and frequently continued despite sterile blood culture [7–10]. The selection of empirical antibiotics varies among countries and regions. Ampicillin in combination with gentamicin is recommended for the management of clinical neonatal sepsis by the World Health Organization (WHO) [11]. However, the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study indicated that in low-income and middle-income countries (LMICs) the use of ampicillin–gentamicin as empirical antibiotics for neonatal sepsis should be reviewed, and potentially replaced with ceftazidime–amikacin [12]. The selection of empirical antibiotics should be based on the common pathogens and related drug susceptibility in each region. The high incidence of sepsis and alarming degree of antimicrobial resistance among pathogens in EOS in neonates underscores the necessity to understand the pathogenesis of early-onset sepsis and to choose the optimum empirical antibiotics.

It is therefore essential to monitor the epidemiology of neonatal EOS regionally to guide the selection of empirical antibiotics. There is a paucity of contemporary, neonatal-specific pathogen distribution and antibiotic susceptibility data for EOS in the northeast of China. The present study aimed to report data for incidence, profile of organisms, and antimicrobial resistance from a prospective cohort study involving 32 newborn intensive care units (NICUs) in China.

METHODS

Study Population

This is a prospective, multicenter, observational cohort study conducted from January 1, 2018 to December 31, 2020. Thirty-two NICUs participated in this study. All infants born at less than
32 weeks of gestation and admitted to NICUs participated in this study within 3 days after birth were included in this study. All infants were followed until death or discharge from the participating NICUs. The studies involving human participants were reviewed and approved by Ethics Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University and Shandong University (LCYJ: NO.2019-132). The ethics committees of all 32 participating hospitals approved the study and allowed data sharing. This study was conducted in accordance with the Declaration of Helsinki.

Date Collection and Quality Management

Detailed maternal intrapartum and newborn information were abstracted from the Sino-northern Neonatal Network (SNN) database. SNN is a large, comprehensive administrative database of preterm inpatients with birthweight (BW) less than 1500 g or gestational age (GA) less than 32 weeks from tertiary hospitals in northern China. Maternal and neonatal information were prospectively recorded into the database by a local neonatologist of 32 NICUs. The aforementioned data sets were collected and transmitted by trained research staff utilizing a standardized manual of operations from each site to the coordinating center in Jinan, Shandong Province, China, and was audited by senior physicians. Maternal data included mother’s age, delivery type, use of antenatal steroid, use of intrapartum antibiotics, rupture of the membranes (ROM) (18 h or more) before delivery. Neonate data included gestational age, birthweight, sex, multiple birth (twin and above), small for gestational age, 1-min and 5-min Apgar score, and fetal tachycardia.

Study Definitions

EOS was defined by the presence of clinical symptoms and a positive culture from blood obtained within 72 h of birth. Gestational age was determined by obstetric estimates. Neonatal necrotizing enterocolitis (NEC) was defined as stage 2 or higher according to the system of Bell et al. [13]. Bronchopulmonary dysplasia (BPD) was defined as mechanical ventilation or oxygen dependency at 36 weeks of postmenstrual age or discharge [14]. Intraventricular hemorrhage (IVH) was defined as stage 3 or higher according to Papile criteria [15]. Retinopathy of prematurity (ROP) was defined as stage 3 or higher according to the International Classification of ROP [16]. Small for gestational age (SGA) was defined as birthweight below the 10th percentile for gestational age on a Fenton growth chart. Extraterine growth retardation (EUGR) was defined according to the 2013 Fenton growth curve, the weight of neonates with gestational age of 36 weeks at discharge or corrected was lower than the 10th percentile of the corresponding gestational age [17].

The definition of contaminant was based on the following three criteria and was similar to in our previous study [18]: (1) isolates which were usually considered as contaminants; (2) coagulase-negative staphylococci (CoNS), when the blood samples were collected there was no peripheral or central catheter; (3) cultures that grew more than one organism.

Multidrug-resistant (MDR) bacteria are defined as non-susceptible to at least one agent in three or more antimicrobial categories [19].

EOS incidence was expressed as the rate of EOS per 1000 infants admitted to the participating NICUs. All-cause mortality was defined as a proportion of neonates deceased among admitted neonates.

Identification and Antimicrobial Susceptibilities Testing

Blood cultures were performed from infants presenting with clinical signs of infection according to clinicians. At least 0.5 ml of blood sample were collected and delivered to the microbiology laboratory within 2 h of collection. Each microbiology laboratory performed organism identification and antimicrobial susceptibility testing (AST). Antimicrobial susceptibilities were classified as susceptible or resistant (intermediate or resistant) based on microbiology reports. Resistance rate was
calculated as the number of resistant pathogens/number of pathogens tested.

**Statistical Analysis**

Descriptive analysis was used to characterize the study population and the pathogen distribution. Numerical data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate and compared using the Student’s *t* test. Categorical data are presented as percentage and analyzed by *χ*². *P* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (SPSS Inc, Chicago, IL).

**RESULTS**

**Maternal and Neonatal Characteristics**

A total of 5865 infants at a GA less than 32 weeks were admitted during the study. The clinical characteristics including maternal and neonatal information are shown in Table 1. Infants with EOS intended to have a lower GA, birthweight, and Apgar scores for 1 min and 5 min than did infants without EOS. Mothers of EOS infants were more likely to have a maternal history of rupture of membranes at least 18 h before delivery. The rate of antenatal steroid use in the EOS group was 85.1%, which was higher than in infants without EOS. Infants with EOS showed significantly higher rates of all-cause mortality and major morbidities, including BPD, IVH, and EUGR.

**Incidence of EOS**

Excluding 28 contaminants, 108 cases of EOS were identified, yielding an incidence of 18.4 cases per 1000 admissions. The incidence rate of EOS increased significantly with decreasing of GA or birthweight (Table 2). The incidence of EOS was highest among infants with a GA of 23–28 weeks (35.8%) and lowest among those with GA of 31–32 weeks (13.5%). The incidence of EOS also increased with the decreasing of birthweight, from 16.3% in the infants with birthweight greater than 1500 g to 23.3% in neonates with birthweight less than 1000 g. The incidence of EOS caused by *E. coli* also significantly increased with the decreasing of GA, while the trend was not distinct with the decreasing of birthweight. EOS caused by GBS was highest in the neonates with GA of 31–32 weeks and infants with birthweight more than 1500 g. Incidence of EOS caused by *Klebsiella* spp. showed no significant difference by GA and birthweight in preterm infants.

**Pathogen Distribution of EOS**

The distribution of pathogens causing EOS is shown in Table 3. The majority of bacterial isolates were Gram-negative pathogens, which accounted for 63.9% of all the pathogens. Gram-positive organisms were identified in 38 of 108 infants. One case had infection with fungal organisms.

*E. coli* was the leading cause of EOS in infants with GA less than 32 weeks, accounting for 40.7% (44/108). *Klebsiella* spp. accounted for 9.3% of EOS cases (10/108). Other Gram-negative bacteria included *Enterobacter* spp. (*n* = 7, 6.5%) and *Serratia marcescens* (*n* = 5, 4.6%). EOS caused by fungi (1, 0.9%) was relatively rare.

In the group of Gram-positive infections, group B streptococci (GBS) were responsible for 7.4% (8/108) of pathogens in preterm infants with EOS. The following two Gram-positive pathogens were *Enterococcus* spp. (*n* = 7, 6.5%) and coagulase-negative staphylococci (*n* = 7, 6.5%).

Figure 1 presents the pathogen distribution according to GA. The types of pathogens causing EOS increased with increasing GA. *E. coli* infection accounted for 75.6% in the group of infants with GA ≤ 28 weeks, while in infants with GA > 30 weeks, the percentage reduced to 16.7%. GBS infection was not found in infants with GA ≤ 28 weeks and the proportion increased with increasing GA.

**Antibiotic Resistance Pattern**

The antibiotic resistance of *E. coli* and *Klebsiella* species to different antibiotics is shown in
Table 4. Within the β-lactam antibiotics, *E. coli* demonstrated maximum susceptibility to meropenem and imipenem and piperacillin-tazobactam while showing high resistance to ampicillin, ceftriaxone, and cefotaxime. *Klebsiella* species showed high resistance to ampicillin, cefotaxime, and ceftriaxone, while they showed high susceptibility to imipenem, meropenem, and piperacillin–tazobactam. Among non-β-lactam antibiotics, *E. coli* showed high resistance to ciprofloxacin and ofloxacin, and high susceptibility to amikacin. All the *Klebsiella* isolates were susceptible to aminoglycosides. Twenty of 33 (60.6%) *E. coli* isolates were multidrug-resistant bacteria according to our predefined definition; 42.9% of *Klebsiella* spp. were multidrug resistant.

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Table 1 Maternal and neonatal characteristics and outcomes of preterm infants enrolled in this study

| Variables               | EOS          | Non-EOS       | P value |
|-------------------------|--------------|---------------|---------|
|                         | *n* = 108    | *n* = 5757    |         |
| Neonatal characteristics |              |               |         |
| Birthweight, g (median, IQR) | 1300 (1100, 1540) | 1370 (1170, 1580) | 0.029   |
| GA, week (median, IQR)   | 29 (28, 30)  | 30 (29, 31)   | 0.001   |
| Apgar 1 min score, mean (SD) | 6.59 (2.48)    | 7.15 (2.30)   | 0.001   |
| Apgar 5 min score, mean (SD) | 7.81 (1.88)    | 8.15 (1.81)   | 0.009   |
| Female, *n* (%)          | 50 (46.3)    | 2261 (51.4)   | 0.164   |
| SGA, *n* (%)             | 5 (4.6)      | 518 (9.0)     | 0.126   |
| Fetal tachycardia, *n* (%) | 4 (3.7)      | 356 (6.2)     | 0.415   |
| Multiple birth, *n* (%)  | 29 (26.9)    | 1358 (23.6)   | 0.425   |
| Maternal characteristics |              |               |         |
| Mother’s age, mean (SD)  | 32 (4.46)    | 31 (8.01)     | 0.494   |
| Caesarean section, *n* (%) | 71 (65.6)    | 3995 (69.4)   | 0.402   |
| Antenatal steroid, *n* (%) | 92 (85.1)    | 4024 (69.9)   | 0.000   |
| Antepartum antibiotic, *n* (%) | 48 (44.4)    | 2245 (39.0)   | 0.274   |
| Rupture of membrane ≥ 18 h, *n* (%) | 26 (24.0)    | 720 (12.5)    | 0.001   |
| Outcome of infants       |              |               |         |
| Mortality, *n* (%)       | 18 (16.7)    | 524 (9.1)     | 0.011   |
| EUGR, *n* (%)            | 48 (44.4)    | 1877 (32.6)   | 0.013   |
| BPD, *n* (%)             | 24 (22.2)    | 524 (9.1)     | 0.000   |
| IVH, *n* (%)             | 6 (5.5)      | 86 (1.5)      | 0.007   |
| NEC, *n* (%)             | 1 (0.9)      | 86 (1.5)      | 1.000   |
| ROP, *n* (%)             | 3 (2.8)      | 391 (6.8)     | 0.119   |

*GA* gestational age, *SGA* small for gestational age, *EUGR* extrauterine growth retardation, *BPD* bronchopulmonary dysplasia, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity
The antibiotic resistance of GBS and *Enterococcus* spp. are listed in Table 5. GBS demonstrated maximum susceptibility to linezolid, vancomycin, and amikacin, while showing high resistance to erythromycin and ofloxacin. *Enterococcus* spp., they showed 100% resistance to erythromycin, 71.4% resistance to ciprofloxacin, 57.1% resistance to ofloxacin, and 100% susceptibility to linezolid and vancomycin. All six *Listeria* isolates were susceptible to ampicillin, erythromycin, linezolid, and vancomycin.

### DISCUSSION

In this real-world study, we record a high incidence of EOS (18.4 per 1000 admissions) among infants with GA less than 32 weeks in 32 NICUs in northern China. The incidence rate of EOS increased with the decreasing of GA and birthweight. *E. coli* and *Klebsiella* spp. emerged as the predominant causative organisms. Most pathogens causing EOS showed an alarming degree of antimicrobial resistance, especially to ampicillin and third-generation cephalosporins. The results of this study have important implications for clinicians who must choose empirical antibiotics for very preterm infants.
Fig. 1 Pathogen distribution and proportion in different GA groups of preterm infants with GA less than 32 weeks.

Table 4. Antimicrobial resistance patterns from the main Gram-negative bacteria of neonates with sepsis, 2018–2020

| Antibiotics          | E. coli n = 44 | % (95% CI) | Klebsiella n = 10 | % (95% CI) |
|----------------------|---------------|------------|-------------------|------------|
| Piperacillin–tazobactam | 2/40          | 5.0 (1.4–16.5) | 3/10              | 30.0 (10.8–60.3) |
| Cefotaxime           | 22/44         | 50.0 (35.8–64.2) | 6/8               | 75.0 (40.9–92.8) |
| Ceftriaxone          | 29/40         | 72.5 (57.1–83.9) | 8/10              | 80.0 (49.0–94.3) |
| Ceftazidime          | 13/40         | 32.5 (20.1–47.9) | 4/10              | 40.0 (16.8–68.7) |
| Imipenem             | 0/39          | 0 (0–8.9)    | 1/10              | 10.0 (1.8–40.4) |
| Meropenem            | 0/37          | 0 (0–9.4)    | 1/10              | 10.0 (1.8–40.4) |
| Ertapenem            | 0/32          | 0 (0–10.7)   | 0/10              | 0 (0–27.8)    |
| Ampicillin           | 35/44         | 79.5 (65.5–88.5) | 9/10              | 90.0 (59.6–98.2) |
| Aztreonam            | 15/35         | 42.9 (27.9–59.1) | 3/10              | 30.0 (10.8–60.3) |
| Amikacin             | 4/44          | 9.1 (3.6–21.2)  | 0/10              | 0 (0–27.8)    |
| Gentamicin           | 15/44         | 34.1 (21.9–48.9) | 4/10              | 40.0 (16.8–68.7) |
| Tobramycin           | 22/44         | 50.0 (34.6–65.4) | 4/8               | 50.0 (21.5–78.5) |
| Ciprofloxacin        | 23/44         | 52.3 (36.9–67.6) | 0/10              | 0 (0–27.8)    |
| Ofloxacin            | 17/40         | 42.5 (26.5–58.5) | 0/10              | 0 (0–27.8)    |

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Incidence rates of EOS vary between countries. The NeonIN study from 30 neonatal units in the UK reported an EOS incidence of 5.6 per 1000 neonate admissions [20]. The rate in Canada was 6.2–6.8/1000 admissions [21]. The rate of EOS reported in Korea among preterm infants less than 32 weeks was 4.1% [22]. A higher EOS rate was reported in a large study among preterm infants conducted in China with 14 cases per 1000 admissions of infants less than 33 weeks' gestation [23]. The current incidence of EOS among infants born at less than 32 weeks of gestation in this prospective study was 18.4 per 1000 admissions. It is worth noting that for this study, the cohort of infants (all preterm infants less than 32 weeks) may be a contributing factor to a higher reported EOS incidence. We have demonstrated that the incidence of EOS was inversely related to GA, which was consistent with previous studies [24, 25].

The pathogen distribution of EOS informs clinicians choice of empirical antibiotics therapy. The pathogen distribution of EOS among different countries was significantly different. The most common pathogens that cause neonatal EOS in four US states from 2005 to 2014 were GBS (36%) and E. coli (25%) [26]. In particular, current reports have shown that there was a marked reduction in EOS caused by GBS, but an increase in E. coli neonatal sepsis [25, 27]. In our previous study, the most frequent pathogens causing EOS were E. coli and GBS in all neonates admitted into 25 NICUs in our multicenter study [18]. While in this study, for infants with GA less than 32 weeks, the predominant organisms were E. coli and Klebsiella spp. Reports have shown that in most LMICs, Klebsiella spp. and E. coli are the most frequent causative organisms [28, 29].

Klebsiella spp., as Gram-negative bacteria, are traditionally considered opportunistic or nosocomial pathogens [30]. In this study, Klebsiella spp. caused 9.3% EOS in very preterm infants. This could possibly be due to very early horizontal transmission in the delivery room or vertical transmission from maternal genital tract colonized with these pathogens after unhygienic personal and obstetric practice [31, 32]. Further investigations are warranted to identify these infections caused by Gram-negative bacteria and subsequently develop targeted prevention strategies. In addition, clinicians should consider empirically treating neonates suspected of EOS empirically with antibiotics predicted to be effective against Klebsiella or Gram-negative pathogens.

| Antibiotics        | GBS n = 8 | % (95% CI) | Enterococcus n = 7 | % (95% CI) |
|--------------------|-----------|------------|--------------------|------------|
| Cefotaxime         | 5/8       | 62.5 (30.5–86.3) | –                  | –          |
| Ceftriaxone        | 6/8       | 75.0 (40.9–92.85) | –                  | –          |
| Ampicillin         | 1/8       | 12.5 (2.2–47.1) | 3/7 (42.9)         | 42.9 (15.8–79.8) |
| Amikacin           | 0/8       | 0 (0–32.4)   | –                  | –          |
| Erythromycin       | 6/8       | 75.0 (40.1–92.9) | 7/7                | 100 (64.6–100) |
| Gentamicin         | –         | –           | 0/8                | 0 (0–32.4) |
| Ciprofloxacin      | 6/8       | 75.0 (40.1–92.9) | 5/7                | 71.4 (35.9–91.8) |
| Ofloxacin          | 4/8       | 50.0 (21.5–78.5) | 4/7                | 57.1 (25.0–84.2) |
| Linezolid          | 0/8       | 0 (0–32.4)   | 0/7                | 0 (0–35.4) |
| Vancomycin         | 0/8       | 0 (0–32.4)   | 0/7                | 0 (0–35.4) |
*E. coli* (40.7%) emerged as the most common isolate in our cohort, which was consistent with findings from LMICs [28, 33]. GBS were isolated rarely in this study. Findings from a few studies from other LMICs also showed similar results [28, 34]. The probably reason may due to limitation in detection methodology, and GBS screening was not widespread in these LMICs [35].

Emergence of antimicrobial resistance has become a global concern. Both the inappropriate overuse of broad-spectrum antibiotics and the inadequacy of antibiotics stewardship led to the increased rate of antimicrobial resistance. Ampicillin resistance among *E. coli* EOS isolates now exceeds 70% [36]. The Centers for Disease Control and Prevention (CDC) and National Institute of Child Health and Human Development (NICHD) studies found 8–10% of EOS *E. coli* isolates to be resistant to both ampicillin and gentamicin [26, 37], a combination frequently used empirically for EOS. A single-center study about the changes in antimicrobial resistance of *E. coli* in eastern China has shown that *E. coli* isolates from preterm infants had a significantly higher rate of resistance to ampicillin, and the overall resistance of *E. coli* to third-generation cephalosporins increased from 14.3% to 46.7% in a decade [38]. In particular, *E. coli* strains causing EOS exhibit a higher resistance to ampicillin, gentamicin, and third-generation cephalosporins in preterm infants than in term infants [29, 38]. In this study, in the infants with GA less than 32 weeks, the resistance rate of *E. coli* to ampicillin was 81.8%, similar to the rate in developed countries. Resistance rates of *E. coli* to third-generation cephalosporins ranged from 32.5% to 72.5%. *E. coli* showed good susceptibility to piperacillin–tazobactam. *Klebsiella* spp., which were the second most common cause of EOS in very preterm infants, also showed high resistance to ampicillin and third-generation cephalosporins. Resistance in *E. coli* and *Klebsiella* spp. is usually acquired via plasmid-mediated extended-spectrum beta-lactamase (ESBL) production [39]. EOS caused by ESBL-producing multidrug-resistant pathogen are resistant to beta-lactams, including third-generation cephalosporins [40]. The very high rates of ESBL production led to a substantial use of carbapenem antibiotics, resulting in the emergence of resistance to carbapenems [41]. Data obtained from China showed that the rate of carbapenem resistance in clinical *E. coli* and *Klebsiella* strains was around 0.6–3.6% and 1.2–18.9%, respectively [42]. The development of rapid diagnostic tests to identify pathogens and their antimicrobial drug susceptibility may therefore prevent unnecessary use of broad-spectrum antimicrobial drugs.

The strength of this study was that it was a real-world study. Detailed maternal and newborn information were prospectively collected from multiple centers covering 32 NICUs in China. This study explored pathogen distribution and the antibiotic resistance pattern in infants with GA less than 32 weeks. Our data raise questions about the empirical use of ampicillin and third-generation cephalosporins for preterm infants with EOS in LMICs. It is of great significance for clinicians who must choose effective antibiotics for neonates suspected of having EOS while awaiting blood culture results to reduce the abuse of antibiotics.

There were some limitations of this study. EOS was defined by positive cultures. Because of the widespread use of intrapartum antibiotics, some infants with true, but culture-negative infection would not have been identified in this study. This was a limitation of all studies that base EOS rates on newborn blood culture results. Another limitation is that the study does not look at the regional differences in incidence and resistance patterns between regions in China.

**CONCLUSION**

*E. coli* and *Klebsiella* spp. were the most common pathogens of EOS of infants with GA less than 32 weeks in China. The incidence of EOS increased with the decreasing of GA or birthweight. *E. coli* and *Klebsiella* spp. showed high resistance to ampicillin and third-generation cephalosporins, which were commonly used for EOS in preterm infants. Our data raise the question about the use of empirical antibiotics for preterm infants with EOS in LMICs. It was
suggested that for preterm infants with EOS, empirical antibiotics should be selected according to the local pathogen distribution and antibiotic sensitivity data.

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**Author Contributions.** Yonghui Yu designed the study and revised the manuscript content. Other authors collected and submitted the data into Shandong Neonatal Network database. Hongyan Ji collected and analyzed the data, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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**Compliance with Ethics Guidelines.** The Institutional Review Board of Shandong Provincial Hospital Affiliated to Shandong First Medical University approved this project (LCYJ: NO.2019-132). The independent ethics committee of each participating hospital approved this study (Shandong Provincial Maternity and Child Health Care Hospital, The First Affiliated Hospital of Shandong First Medical University, Jinan Maternity and Child Health Care Hospital, Yantai Yuhuangding Hospital, Affiliated Hospital of Weifang Medical University, Weifang Maternal and Child Health Hospital, Linyi People’s Hospital, Women and Children’s Healthcare Hospital of Linyi, Taian City Central Hospital, Liaocheng People’s Hospital, Binzhou Medical University Hospital, Taian Maternal and Child Health Care Hospital, Dongying People’s Hospital, Dongying, The Second Affiliated Hospital of Shandong First Medical University, Jinan Central Hospital, The Second People’s Hospital of Liaocheng, Liaocheng, People’s Hospital of Rizhao, Jinan Second Maternal and Child Health Care Hospital, Central People’s Hospital of Tengzhou, Juxian Peoples Hospital, Liaocheng Dongchangfu Maternal and Child Health Hospital, Zibo Maternal and Child Health Hospital, Dezhou Peoples Hospital, Heze Municipal Hospital, Hebei Petro China Central Hospital, Weifang Yidu Central Hospital, Yantai Yantaishan Hospital, Baogang Third Hospital of Hongci Group, Shengli Oilfield Central Hospital). All authors have signed written informed consent and approved the submission of this version of the manuscript and take full responsibility for the manuscript. The legal guardian of all participants signed an informed consent form that their data could be used for various clinical studies.

**Data Availability.** The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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