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ORIGINAL RESEARCH

Multi-Drug Resistant *Escherichia coli* Causing Early-Onset Neonatal Sepsis – a Single Center Experience from China

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Background and objective: Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) have raised public-health concerns and are becoming a global health challenge. This study aimed to investigate changes in antimicrobial resistance of *E. coli* responsible for early-onset sepsis (EOS) in a perinatal center in eastern China.

Methods: Two periods, 2002 to 2008 and 2012 to 2018, were investigated. EOS was defined as the presence of a single potentially pathogenic bacterium grown from blood or cerebrospinal fluid in cultures drawn in any newborn infant within 72 hrs of birth. The changes in antimicrobial resistance of *E. coli* were analyzed.

Results: A total of 163 cases of EOS were identified, and *E. coli* continued to be the leading pathogen in our neonatal intensive care unit (NICU). Overall resistance of *E. coli* to third-generation cephalosporins increased from 14.3% in 2002–2008 to 46.7% in 2012–2018 ($p<0.05$). This resistance pattern closely parallels ESBL production. Compared to that from term infants, *E. coli* isolated from preterm infants had a significantly higher rate of resistance to ampicillin (93.3% vs 48.4%, $p<0.01$) and gentamicin (60.0% vs 9.4%, $p<0.01$), as well as a higher rate of ESBL production (66.7% vs 15.6%, $p<0.01$).

Conclusion: We conclude that ESBL-producing multi-drug resistant *E. coli* has emerged as the major pathogen responsible for early-onset neonatal sepsis, particularly in preterm infants. Clinicians should consider this trend and attempt to select proper effective antibiotics as the empirical treatment for early-onset neonatal sepsis.

Keywords: *Escherichia coli*, extended-spectrum beta-lactamase, early-onset sepsis, neonatal intensive care unit, newborn

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Introduction

Neonatal sepsis remains a major cause of neonatal morbidity and mortality despite significant advances in perinatal care over the last few decades.[1] Early-onset sepsis (EOS) which is defined as infection occurring within 72 hrs after birth is usually acquired through the vertical transmission of organisms from mother to infant. The overall incidence of culture-confirmed EOS in industrialized countries is reported to be 0.54–0.9 per 1000 live births.[2–4] The reported incidence of culture-confirmed EOS from low- and middle-income countries appears to be higher.[5,6] The presence of maternal risk factors such as prolonged rupture of membranes (PROM), chorioamnionitis and premature delivery is usually associated with a higher incidence of EOS in neonates. *Group B Streptococcus* (GBS) and *Escherichia coli* (*E. coli*) are

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the two most common pathogenic organisms for EOS.[5,7] To prevent EOS due to GBS, either a risk-based approach to identify women who may benefit from intrapartum antimicrobial prophylaxis (IAP) or the administration of IAP to all colonized women based on the result of universal antenatal screening for GBS at 35 to 37 weeks' gestational age has been recommended and implemented in most countries.[2,3]

Symptoms of EOS are usually non-specific and most neonatologists start empiric antibiotics when EOS is suspected, prior to the availability of blood culture results. Selection of appropriate initial empiric antibiotics is based mainly on the sensitivity patterns of GBS and *E. coli* in different hospitals and regions since these are the two most common organisms. Limited data are available from low- and middle-income countries on the epidemiology and antimicrobial resistance patterns of EOS, particularly from China where dramatic socioeconomic changes have occurred in the last two decades due to industrialization. While reports of EOS due to GBS in China are relatively rare,[8] all report GBS isolates from Chinese neonates thus far are susceptible to penicillin.[9–11] On the other hand, our recent meta-analysis based on a systematic review of the published studies in Chinese literature demonstrates that in newborn infants hospitalized in Chinese NICUs, roughly 50% of all *E. coli* bloodstream isolates (regardless of early onset or late onset) are multi-drug resistant due to extended-spectrum beta-lactamase (ESBL) production.[12] Therefore, the objective of this study was to investigate changes over time of the clinical characteristics and antimicrobial resistance patterns of EOS caused by *E. coli* in a tertiary neonatal intensive care unit in eastern China. This may contribute to a more informed selection of appropriate antibiotics for empirical therapy in developing countries with similar bacterial profile and sensitivity patterns.

Materials and Methods

Data Collection

All newborn infants admitted into the neonatal intensive care unit (NICU) of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University with a diagnosis of EOS were included in this retrospective cohort study. EOS was defined as the presence of a single potentially pathogenic bacterium grown from blood or cerebrospinal fluid (CSF) in cultures drawn in any newborn infant within 72 hrs of birth. The sensitivity/specificity test results and ESBL status were obtained from our clinical laboratory reports. The clinical laboratory in our center practices routine microbiological tests according to the standard set by the Clinical & Laboratory Standards Institute (USA). Due to the long time span covered in this study, either the conventional biochemical techniques or automated methods with the VITEK system (Vitek 2 compact, BioMerieux, France) was used to identify the specific bacterial species. Initially, the manual Kirby-Bauer disc diffusion method or more recently the Gram-Negative Susceptibility card (BioMerieux, France) was utilized to determine antibiotic susceptibility of bacterial isolates. Two periods, 2002 to 2008 and 2012 to 2018, were covered in the study. All cases were identified from a registry and hospital records of diagnosis with a confirmation from a detailed chart review.

Demographics and relevant clinical data were collected from the medical records. We collected the information about the birth place (inborn or outborn), gestational age, mode of delivery, prolonged rupture of membranes (PROM>18 hrs), intrapartum fever (>38ºC), and the use of antepartum antibiotics. Data related to infants such as gender, birth weight, clinical symptoms such as respiratory distress, septic shock and meningitis were also collected. To calculate the incidence of EOS, data on the number of total live births in the hospital during these two periods were also collected. The Institutional Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University approved the study protocol. A waver for patient parental consent to review their medical records was granted by the Institutional Ethics Committee. The handling of the patient data confidentiality strictly followed the rules set by the institution and were in compliance with the Declaration of Helsinki.

Statistical Analysis

SPSS 24.0 software was used to perform the statistical analysis. The basic clinical characteristics and the results of blood culture and antimicrobial susceptibilities were analyzed. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed data are described as the mean ± standard deviation (M ±SD) and were analyzed using Student's *t*-test. Non-normally distributed data are described as median and range and were analyzed using the Wilcoxon signed rank test or the Mann–Whitney *U*-test. Categorical data were analyzed using the Chi-square test or Fisher's exact test. The incidences of EOS were calculated by dividing the

number of inborn infants with EOS by the number of live births in the hospitals. A p-value of < 0.05 for the predictive variables was considered significant.

Results

The total number of live births was 27,522 in 2002–2008 and 58,619 in 2012–2018, respectively, in the study hospital. A total of 163 cases of culture-confirmed EOS were identified. Of these, 65 were from years 2002–2008 and 98 were from years 2012–2018. Of the 163 cases, 46 infants (5 from 2002–2008 and 41 from 2012–2018) who were inborn developed EOS, and the other 117 cases were either transferred from other hospitals that did not have NICU services or directly admitted from the community after home birth. Therefore, the calculated incidence of culture-confirmed EOS in the inborn infants was 0.18 per 1000 live-births in 2002–2008 and 0.70 per 1000 live-births in 2012–2018.

Table 1 illustrates the distribution of bacterial pathogens for EOS in 2002–2008 and 2012–2018. *E. coli* continued to be the leading bacterial pathogen for EOS despite GBS emerging as equally important in 2012–2018. The proportion of *E. coli* as the pathogen in EOS remained relatively stable over the last two decades, while GBS became the most frequently isolated Gram-positive bacteria in 2012–2018.

Table 2 shows the general characteristics of patients with early-onset *E. coli* sepsis from 2002 to 2008 and 2012 to 2018. Compared with 2002–2008, children with early-onset *E. coli* sepsis from 2012 to 2018 were born at an earlier gestational age and with lower birth weight (P<0.001 and P<0.05, respectively), and their mothers were older as well (P<0.05). A significantly higher proportion of preterm infants or low birth infants were diagnosed with early-onset *E. coli* sepsis from 2012 to 2018 compared to 2002–2008. The number of early-onset *E. coli* sepsis infants whose mothers were treated with antepartum antibiotics was also significantly increased in 2012–2018 (P<0.01).

Table 1 Distribution of Pathogens of EOS in 2002–2008 and 2012–2018

Pathogens	2002–2008 (n = 65)	2012–2018 (n = 98)
Gram-positive organisms		
GBS	0 (0%)	26 (26.5%)*
CoNS	13 (20.0%)	12 (12.2%)
Enterococcus	6 (9.2%)	11 (11.2%)
Staphylococcus aureus	2 (3.1%)	6 (6.1%)
Listeria monocytogenes	1 (1.5%)	3 (3.1%)
Other	8 (12.3%)	8 (8.2%)
Gram-negative organisms		
E coli	21 (32.3%)	26 (26.5%)
Klebsiella	5 (7.7%)	2 (2.0%)
Other	9 (13.8%)	4 (4.1%)

Notes: *$\chi 2$ = 20.518, P < 0.001.

Table 2 General Characteristics of Patients with Early-Onset *E. coli* Sepsis

	2002–2008 (n = 21)	2012–2018 (n = 26)	*P*-value
Male gender	14 (66.7%)	15 (57.75%)	N.S.
Gestational age (weeks)	39.3 ± 1.9	35.8± 4.6	0.001
<37 weeks	2 (9.5%)	13 (50.0%)	0.003
Birth weight (gm)	3125 ± 563	2648 ± 960	0.040
<2500 gm	2 (9.5%)	12 (46.2%)	0.006
Maternal age (years)	26.8 ± 5.2	30.0 ± 5.7	0.047
Vaginal delivery	20 (95.2%)	22 (84.6%)	N.S.
PROM>18hrs	3 (14.3%)	10 (38.5%)	N.S.
Intrapartum fever	1 (4.8%)	5 (19.2%)	N.S.
Antepartum antibiotic	0 (0%)	9 (34.65%)	0.009
Home delivery	4 (19.0%)	1 (3.8%)	N.S.
Respiratory distress	4 (19.0%)	9 (34.6%)	N.S.
Shock	2 (9.5%)	2 (7.7%)	N.S.
Meningitis	4 (19.0%)	3 (11.5%)	N.S.
Death	2 (9.5%)	4 (15.4%)	N.S.

Note: *P < 0.05.
Abbreviation: NS, not significant.

The changes in antibiotic susceptibility for all *E. coli* isolated from infants with EOS in 2002–2008 and 2012–2018 are presented in Figure 1. As the figure shows, overall resistance of *E. coli* to third-generation cephalosporins increased from 14.3% in 2002–2008 to 46.7% in 2012–2018 (p<0.05). This resistance pattern closely paralleled to ESBL production which increased from 13.3% in 2002–2008 to 46.2% in 2012–2018 (p<0.05). The resistance of *E. coli* to ciprofloxacin increased from 9.5% in 2002–2008 to 38.5% in 2012–2018 (p<0.05). Although 73.1% of *E. coli* isolates in 2012–2018 were ampicillin-resistant, while 50.0% were ampicillin-resistant in 2002–2008, this difference was not statistically significant. The incidence of resistance of *E. coli* to gentamicin remained relatively unchanged (23.8% in 2002–2008 vs 26.9% in 2012–2018, p>0.05).

Figure 2 shows the results of antibiotic susceptibility testing on *E. coli* causing EOS grouped by term vs preterm infants. Compared to that from term infants, *E. coli* isolated from preterm infants had a significantly higher rate

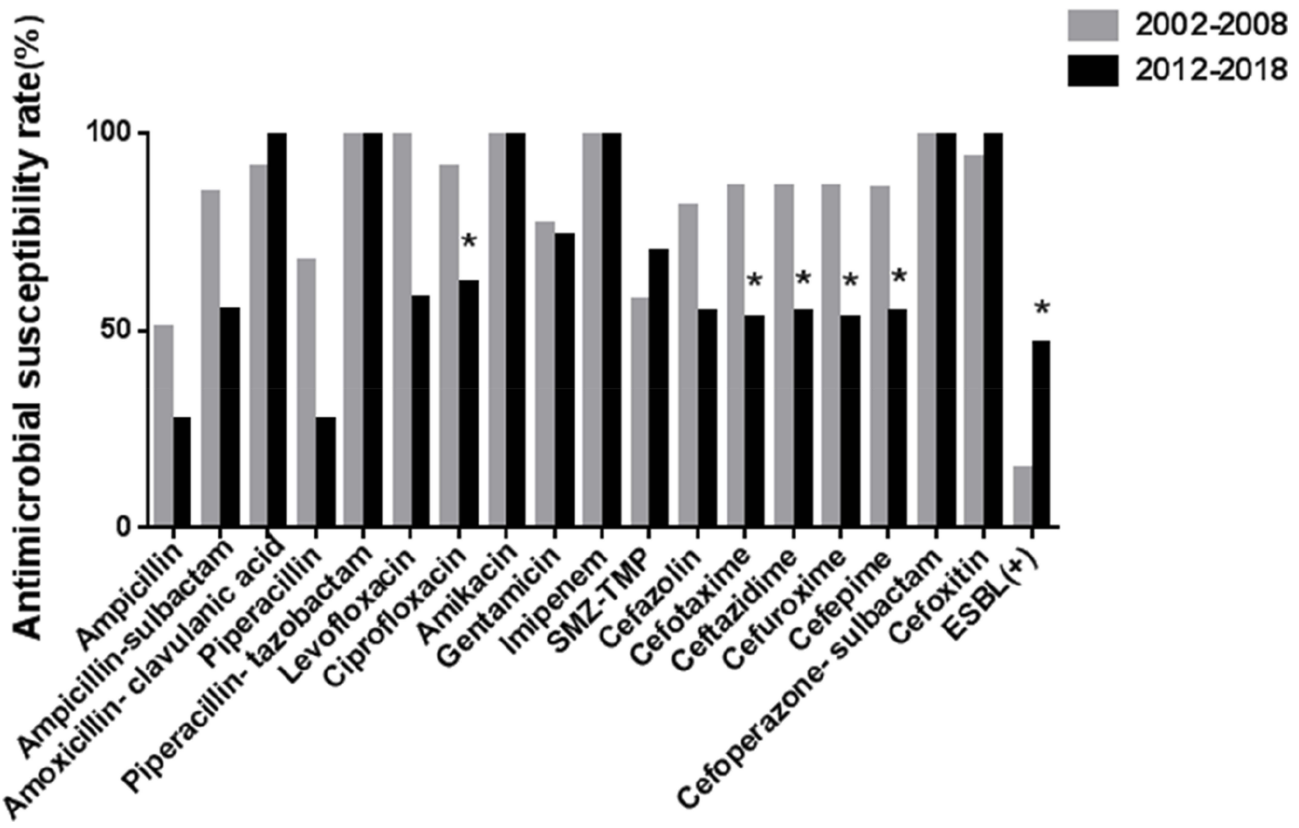

Figure 1 Antimicrobial susceptibility of all isolated *E. coli* in 2002–2008 and 2012–2018. *$P < 0.05$.

of resistance to both ampicillin (93.3% vs 48.4%, $p<0.01$) and gentamicin (60.0% vs 9.4%, $p<0.01$). Two-thirds of *E. coli* (66.7%) isolated from preterm infants was resistant to third-generation cephalosporins, which is significantly higher than those isolated from term infants (15.6%, $p<0.001$). This resistance difference is mainly due to ESBL-producing *E. coli* which represented 66.7% of all *E. coli* isolated from preterm infants as compared to 15.6% of *E. coli* in term infants ($p<0.001$). Overall, almost all isolated *E. coli* from EOS infants from our NICU were still susceptible to amoxicillin-clavulanic acid, piperacillin-tazobactam, amikacin, cefoxitin, and imipenem.

Discussion

EOS is mainly caused by vertical transmission of organisms from mother to infant during labor and delivery.[2–5] The most recent guidelines for the management of EOS are based on epidemiologic studies that are from industrialized countries.[13,14] Data about EOS from developing countries are relatively rare, and the bacterial profile may be significantly different.[6] The current study from a large tertiary perinatal center in eastern China demonstrates that the current incidence of culture-confirmed EOS is around 0.7 per 1000 live-births. *E. coli* remains the leading bacterial pathogen for EOS despite GBS emerging as equally important in recent years. Although the proportion of *E. coli* as the pathogen for EOS has remained relatively stable over the last 2 decades, increasing numbers of multi-drug resistant *E. coli* due to ESBL production are being isolated as the responsible pathogen in at least one NICU in eastern China. This poses a serious challenge concerning the selection of appropriate antibiotics for empirical therapy.

Despite a relative low incidence, EOS accounts for approximately 16% of all neonatal mortality.[3] While GBS remains the most common etiologic agent for EOS in industrialized countries, *Staphylococcus* and gram-negative bacteria such as *Klebsiella* and *E. coli* are the most frequent causative organisms responsible for EOS in most low- and middle-income countries.[6,15] In the last decade, the annual deliveries in our hospital have increased significantly. This has made our center one of the largest perinatal centers in eastern China where dramatic socioeconomic changes have occurred due to industrialization. The incidence of culture-confirmed EOS from our inborn infants now appears to be comparable to that

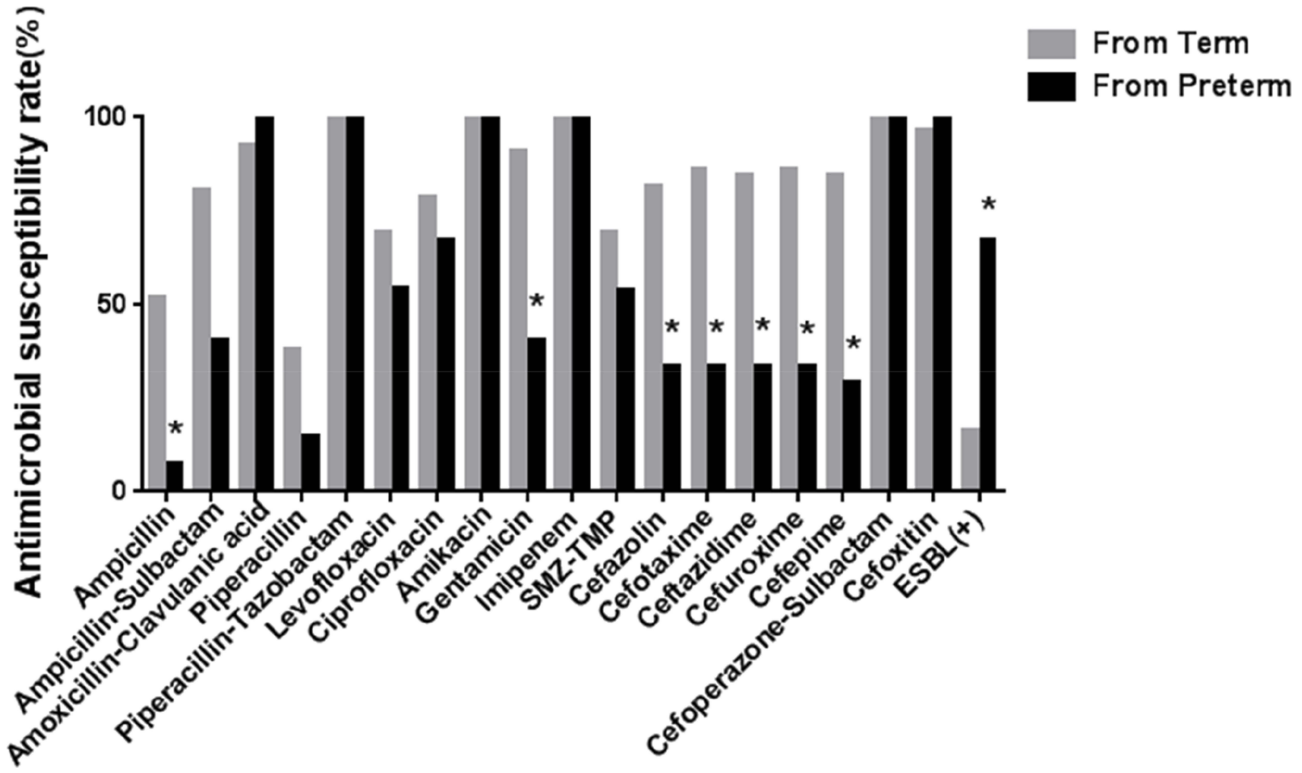

Figure 2 Antimicrobial susceptibility of all isolated *E. coli* from term and preterm infants.

reported from industrialized countries in the range of 0.54–0.9 per 1000 live births.[2–4] Interestingly, along with the industrialization in the region, the pathogen profile for EOS in our center has also changed to that similar to those reported from developed countries. In addition to *E. coli*, GBS has now emerged to be equally important as the pathogen for EOS.

EOS due to *E. coli* usually has a higher mortality rate than that caused by gram-positive bacteria.[16] The incidence of invasive early-onset GBS disease in developed countries has significantly decreased due to the implementation of IAP guidelines.[17] However, the widespread use of IAP for GBS disease has led to concerns about a potential adverse impact on *E. coli* incidence. Indeed, in an epidemiologic study from the United States, although the overall incidences of EOS due to *E. coli* over the last decade remained relatively stable, *E. coli* cases were found to be more common than GBS in some region.[7] Early-onset *E. coli* sepsis is more common in premature and very low birth weight infants and is more likely to be associated with intrapartum fever, preterm premature rupture of membranes, PROM, antibiotic use, and sepsis onset on the first day of life.[7,18] In our study, we found that when compared to those of the year 2002–2008, infants with early-onset *E. coli* sepsis from years 2012–2018 were more likely to be premature, have lower birth weight, and have received IAP. Our results are consistent with the previous findings that prematurity has become one of the most important risk factors for early-onset *E. coli* infection.[8]

Roughly 50% of *E. coli* bloodstream isolates (regardless of early onset or late onset) from Chinese NICUs are multi-drug resistant due to ESBL production.[12] In the current study, among all *E. coli* isolates from infants with EOS in 2012–2018, 73.1% are ampicillin-resistant and 46.7% are resistant to third-generation cephalosporins, which are significantly higher than the percentages of resistance from 2002 to 2008. Our data indicate that increasing numbers of ESBL-producing multi-drug resistant *E. coli* are being isolated as the pathogens responsible for EOS. The changing patterns of antibiotic susceptibility for all *E. coli* isolated from infants with EOS in China are very worrisome. Our results indicate that the prevalence of multi-drug resistant *E. coli* isolated from infants with EOS in our NICU is much higher than that from the United States, where a high rate of ampicillin resistance, no aminoglycoside resistance, and a very low rate of resistance to third-generation cephalosporins are reported.[19] On the

other hand, the antimicrobial resistance pattern in India appears to be even worse based on a recent report.[15] Almost half of the *E. coli* isolates from newborn infants in Delhi are resistant to commonly used third generation of cephalosporins. Moreover, 15% of their *E. coli* isolates are even carbapenem resistant, which is not the case for our isolates. Data obtained from the China Antimicrobial Resistance Surveillance Report show that the rate of carbapenem resistance in clinical *E. coli* strains is around 0.6–3.6% in different provinces of China.[20] All isolated *E. coli* from EOS infants in our NICU thus far are still carbapenem susceptible.

We have previously speculated that ESBL-producing multi-drug resistant gram-negative bacterial infections in Chinese NICUs are likely due to unrestricted use in neonates of broad-spectrum antibiotics, especially third generation of cephalosporins.[12] This may be true for late-onset sepsis caused by multi-drug resistant bacteria. Clearly, causes other than NICU practice were responsible for the fact that ESBL-producing *E. coli* has emerged as the main pathogen for EOS in our NICU. There are several studies that have demonstrated the relationship between the antibiotic chosen for IAP and resistant *E. coli* infections in neonates.[21,22] Colonization of resistant bacteria in pregnant women during hospitalization may be another reason. Indeed, significantly higher numbers of ESBL-producing *E. coli* were isolated from premature infants as demonstrated in the current study. A higher percentage of resistance to ampicillin, gentamicin, and third-generation cephalosporins was observed among *E. coli* strains causing EOS from preterm infants in comparison with those from term infants. In the current study, the median hospitalization days prior to delivery in women with preterm delivery were 1 (range 0–11 days) which was significantly longer than those with term delivery (median=0, range 0–0, $p<0.001$). Therefore, the mothers of preterm infants were at higher risk of being exposed and colonized with resistant *E. coli* prior to delivery.

Globally, ESBL-producing *E. coli* infection has been increasingly reported with evidence of spread in the community.[23,24] An increasing proportion of ESBL-producing *E. coli* among patients without any healthcare risk factors was observed in South Korea.[24] In a report from Japan, 26.3% patients with ESBL-producing *E. coli* infection were considered to be community-associated because there were no discernible healthcare-associated risk factors.[25] Community-associated infections caused by ESBL-producing *E. coli* have already raised public-health concerns and are gradually becoming a clinical challenge.[26] Infections with community-associated ESBL-producing *E. coli* in China are not rare.[27] In a recent study from China, a surprisingly high number (50.5%, 55/109) of fecal samples from healthy adults showed the presence of ESBL-producing *E. coli*.[28] Even some (2.8%) of *E. coli* isolates obtained from rivers and lakes in Northwest China were found to be ESBL producers.[29] This is because a significant increase in antibiotic consumption has been seen in China and other developing countries both as prescriptions for patients and feed additives in the agriculture industry.[30] Such unrestricted use of antibiotics has exerted strong selective pressure in the environment for resistant bacteria, especially for zoonotic pathogens such as *E. coli*. Mounting scientific evidence has shown that 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 human beings.[31] Vaginally delivered neonates are colonized first with maternal fecal and vaginal flora. Therefore, high prevalence of ESBL-producing *E. coli* colonization in pregnant mothers in China may be another explanation for the fact that increasing numbers of ESBL-producing multi-drug resistant *E. coli* are being identified as the pathogen for early-onset sepsis in our NICU.

In summary, we have focused on the changing pattern of antimicrobial resistance of *E. coli* responsible for early-onset neonatal sepsis in a perinatal center in eastern China and found that ESBL-producing multi-drug resistant *E. coli* has emerged as a main pathogen responsible for early-onset neonatal sepsis in our region. Although the trend of increasing antibiotic resistance of *E. coli* is threatening the entire global population, it is more so to neonates since neonatal sepsis remains a major cause of neonatal mortality, especially in developing countries. Continuous surveillance for antibiotic susceptibility is needed to ensure proper empirical therapy. It is critical for clinicians to consider this trend and attempt to select proper effective antibiotics as the empirical treatment for early-onset neonatal sepsis.

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Disclosure

The authors report having no conflicts of interest relevant to this article to disclose.

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