Pathogens Responsible for Early-Onset Sepsis in Suzhou, China

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SUMMARY: Early-onset sepsis (EOS) in neonates is a serious disease with severe complications. The increased severity of EOS and risk of death in newborns in recent years signify that continued monitoring to detect possible changes in the pathogen etiology, disease severity, and disease outcome is particularly important. We conducted a retrospective study on early-onset infection among infants (birth weights > 800 g) who were hospitalized in the Children’s Hospital of Soochow University from January 1, 2011, to December 31, 2017. Multivariable analysis was performed to determine the significant predictors of mortality. The most frequent early-onset pathogen was Group B Streptococcus (GBS) (28.1%), followed by Escherichia coli (21.6%), Listeria monocytogenes (11.8%), and Klebsiella pneumoniae (7.8%). Most infants (85.6%) with early-onset infections survived until hospital discharge, while 44 (14.4%) patients died. Multivariable logistic regression analysis showed that the significant predictors of mortality were the pathogen (GBS, E. coli, or other pathogens) and birth weight (both \( P < 0.01 \)). GBS remains the most frequent pathogen known to infect infants. E coli was the most common pathogen associated with neonatal mortality. Prevention of E. coli sepsis, specifically among preterm infants, remains a challenge.

INTRODUCTION

Early-onset sepsis (EOS) in neonates is a serious disease with severe complications. The epidemiology of EOS has changed over the last decades. Following the 1970s, Group B Streptococcus (GBS) was the leading cause of EOS(1). To prevent GBS infections, national programs including the intrapartum use of antibiotics, have been designed to reduce the vertical transmission of GBS, and a reduction in the incidence of early-onset GBS sepsis was reported during the 1990s(2,3). However, an increase in the incidence of early-onset Escherichia coli sepsis has occurred during the same time period(4). Several studies have found that the incidence of early-onset E. coli sepsis has continued to increase over the last decades, and this has manifested itself as increased disease severity and risk of newborn death(5–7).

The increased severity of EOS and risk of death for newborns in recent years signify that continued monitoring to detect possible changes in pathogen etiology, disease severity, and disease outcome is particularly important. In China, comprehensive studies on EOS are rare. Therefore, in the present study, we investigated the epidemiology of early-onset sepsis among infants born in Suzhou, China, over a 7-year period.

MATERIALS AND METHODS

We conducted a retrospective study on EOS and EO meningitis (EOM) among infants (birth weights > 800 g) who were hospitalized at the Children’s Hospital of Soochow University from January 1, 2011, to December 31, 2017. Early-onset infection was defined as the presence of EOS and/or EOM(8). EOS was defined by the isolation of a pathogen in a blood culture from samples drawn within 72 h of birth, while EOM was defined as a pathogen isolated from cerebrospinal fluid (CSF) cultures and/or CSF pleocytosis (defined as the condition in which infants have > 30 white blood cell counts and < 45,000 red blood cell count in the CSF) within 72 h of birth (8,9). Coagulase-negative Staphylococci, Micrococci, Propionibacteria, Corynebacteria, or Diphtheroids that grown alone or CSF pleocytosis (defined as the condition in which infants have > 30 white blood cell counts and < 45,000 red blood cell count in the CSF) within 72 h of birth (8,9). Coagulase-negative Staphylococci, Micrococci, Propionibacteria, Corynebacteria, or Diphtheroids that grown alone or CSF pleocytosis (defined as the condition in which infants have > 30 white blood cell counts and < 45,000 red blood cell count in the CSF) within 72 h of birth (8,9).

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 17.0). Data were expressed as numerical values with percentage, mean, and standard deviation or median and interquartile range, as appropriate. Normally distributed continuous variables were compared using the Student’s t-test, and non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical data were
analyzed using the chi-squared ($\chi^2$) test or Fisher’s exact test. Univariate differences were assessed by $\chi^2$ for categorical variables and by the Kruskal-Wallis test for continuous variables. Multivariate analysis was performed using backward stepwise logistic regression, starting with all univariate factors that were significant at $P < 0.1$.

**RESULTS**

Between January 2011 and December 2017, 352 infants aged $\leq 72$ h with positive cultures were identified at the Children’s Hospital of Soochow University. Overall, 46 infants with positive cultures that were considered to be composed of contaminants were excluded from any further analyses. EOS and/or EOM was diagnosed in 306 infants, of whom 178 (58.2\%) were preterm (gestational age, $< 37$ weeks) and 172 (56.2\%) were male. The demographic characteristics of the neonates are shown in Table 1.

Table 1. Demographic characteristics of the 306 cases with early onset sepsis

| Characteristic                  | Number (%) |
|--------------------------------|------------|
| Sex                            |            |
| Male                           | 172 (56.2) |
| Female                         | 134 (43.8) |
| Gestational age                |            |
| $< 37$ wk                      | 178 (58.2) |
| $\geq 37$ wk                   | 128 (41.8) |
| Birth weight                   |            |
| $< 1,500$ g                    | 66 (21.6)  |
| 1,500–2,500 g                  | 94 (30.7)  |
| 2,500–4,000 g                  | 126 (41.2) |
| $\geq 4,000$ g                 | 20 (6.5)   |
| Cesarean delivery              | 185 (60.4) |
| Multiple gestation             | 12 (3.9)   |
| Membrane rupture $\geq 18$ h before delivery | 112 (36.6) |
| Exposure to intrapartum antibiotics | 94 (30.7) |
| Pregestational diabetes mellitus | 38 (12.4) |
| Maternal intrapartum fever     | 57 (18.6)  |

Table 2. Distribution of pathogens among 306 cases of early onset sepsis

| Organism                  | Number with Sepsis (%) |
|---------------------------|------------------------|
| Gram-negative organisms   |                        |
| *Escherichia coli*        | 66 (21.6)              |
| *Klebsiella pneumoniae*   | 24 (7.8)               |
| *Pseudomonas aeruginosa*  | 10 (3.3)               |
| Other gram-negative$^1$   | 22 (7.2)               |
| Gram-positive organisms   | 174 (56.9)             |
| *Group B streptococcus* (GBS) | 86 (28.1) |
| *Listeria monocytogene*   | 36 (11.8)              |
| *Staphylococcus haemolyticus* | 12 (3.9)  |
| *Staphylococcus hominis*  | 10 (3.3)               |
| Other gram-positive$^2$   | 30 (9.8)               |
| Fungi                     | 10 (3.3)               |
| *Candida albicans*        | 10 (3.3)               |
| Total$^3$                 | 306 (100)              |

$^1$: Organisms found in blood culture: *Enterobacter cloacae* in 6 cases; *Morganella* species in 6 cases; *Haemophilus* in 4 cases; *Moraxella* species in 4 case; *Acinetobacter* species in 2 case.

$^2$: Organisms found in blood culture: *S aureus* in 8 cases; *Streptococcus mitis* in 6 case; *Streptococcus gordonii* in 6 case; *Streptococcus cohnii* in 4 case; *Streptococcus oralis* in 4 case; *Streptococcus anginosus* in 2 case.

$^3$: Among the 306 patients, 30 patients had early onset sepsis meningitis (EOM). Of the 30 patients with EOM, 22 had blood and CSF cultures that were positive for the same organism: *Klebsiella pneumoniae* in 6 cases; *Escherichia coli* in 6 cases; *GBS* in 6 cases; *Staphylococcus hominis* in 4 cases; and 8 infants had negative blood cultures and positive CSF cultures: 2 each for *GBS; Klebsiella pneumoniae; Escherichia coli* and *Listeria monocytogene*.

were preterm (gestational age, $< 37$ weeks) and 172 (56.2\%) were male. The demographic characteristics of the neonates are shown in Table 1.

**Pathogen distribution:** Of the 306 infants confirmed to have early-onset infections, 220 (72.9\%) underwent a lumbar puncture. Pathogens were isolated from the CSF of 30 infants who underwent lumbar puncture. Of the 30 patients with EOM, 22 had blood and CSF cultures that...

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Fig. 1. Distribution of the organisms among full-term and preterm infants with early onset infections.
were positive for the same organism, while 8 infants had negative blood cultures and positive CSF cultures.

Nearly half of the early-onset infections were caused by Gram-positive organisms (Table 2). The most frequent early-onset pathogen was GBS (28.1%), followed by E. coli (21.6%), Listeria monocytogenes (11.8%), and Klebsiella pneumoniae (7.8%). Fungal infections were found in only 10 (3.3%) of the patients.

The distribution of the organisms among the full-term and preterm infants is shown in Fig. 1. GBS was responsible for the majority of infections among the full-term patients (32.8%), followed by E. coli (22.1%), and L. monocytogenes (10.1%). Among the preterm infants, GBS and E. coli were again the most common pathogens, accounting for 18.3% and 18.1%, respectively, followed by L. monocytogenes (12.1%) and K. pneumoniae (10.2%). GBS was more commonly detected and K. pneumoniae was less commonly detected in the full-term infants than in the preterm patients (both P < 0.01).

We also compared the distribution of organisms in infants hospitalized between 2011–2013 and 2014–2017 (Fig. 2). During 2011–2013, GBS was the most frequent cause of EOS (25.3%), and L. monocytogenes infections were rare (2.2%). In 2014–2017, the percentages of GBS, E. coli, and L. monocytogenes were similar.

Antibiotic susceptibility: Information on antibiotic sensitivity was available for 280 of the 306 infants. All of the tested GBS isolates were sensitive to penicillin, ampicillin, and vancomycin; however, 54% were resistant to erythromycin and 33% to clindamycin. Among the tested E. coli isolates, all were sensitive to amikacin, nitrofurantoin, pipercillin/tazobactam, cefoperazone/sulbactam, cefoxitin, and imipenem, whereas all of them were resistant to levofloxacin. Enterobacteriaceae isolates, including E. coli, Klebsiella oxytoca, K. pneumoniae, and Proteus mirabilis, were also evaluated for extended-spectrum beta-lactamase (ESBL), and 40.9% (38/93) of Enterobacteriaceae isolates were identified as ESBL Enterobacteriaceae. Among the tested ESBL Enterobacteriaceae isolates, all were sensitive to piperacillin/tazobactam and cefoperazone/sulbactam; however, all were resistant to ceftriaxone and 76.3% of them were resistant to ceftazidime.

Infant antibiotic therapy: The majority of the infants with infections (83%) were initially administered cephalosporins, while 11% received amoxicillin. After identifying the pathogen and its antibiotic susceptibility profile, antibiotics were changed in 42% of the infants. Vancomycin, cefoperazone sulbactam, and meropenem were the most frequently substituted antibiotics. Among the 174 infants with Gram-positive bacterial infections, the majority, 75%, continued receiving cephalosporins or amoxicillin once the culture results were available, whereas 12% switched to vancomycin with or without continuation of the initially prescribed antibiotics. Among the 122 infants who tested positive for Gram-negative organisms, 48% had their initial antibiotic therapies continued, whereas 32% switched to meropenem or cefoperazone sulbactam.

Risk factors for mortality: Most infants (85.6%) with early-onset infections survived until hospital discharge, while 44 (14.4%) patients died; 24 (54.5%) of the deaths occurred during the first 3 days of life, 10 (22.7%) occurred during the first 4 to 7 days of life, while another 10 (22.7%) deaths occurred afterward. Of the 44 patients, E. coli was detected in 16 (36.4%), and L. monocytogenes in 14 (31.8%) patients, while GBS was detected in only 2 (4.5%) patients.

In the univariate analysis, mortality was associated with the pathogen (GBS, E. coli, or other pathogens), birth weight, gestational age, and exposure to intrapartum antibiotics (all P < 0.01, Table 3). Multivariate logistic regression analysis showed that the significant predictors of mortality were the pathogen (GBS, E. coli, or other pathogens) and birth weight (both P < 0.01). The odds of death among infants with E. coli infection were significantly higher than those among infants with GBS infection (odds ratio [OR], 8.3; 95% confidence interval [CI], 3.5–22.1), consistent with the odds of death among infants with other pathogens compared with those with GBS infection (OR, 5.5; 95% CI, 2.4–11.8). The odds of death among infants with birth weight < 1,500 g were significantly higher than those among infants with birth weight ≥ 1,500 g (OR, 18.5; 95% CI, 9.3–24.7).
Pathogens of Early-Onset Sepsis

| Characteristic                        | Died (n = 44), n (%) | Survived (n = 262), n (%) | P value |
|--------------------------------------|----------------------|---------------------------|---------|
| Pathogen                             |                      |                           |         |
| GBS                                  | 2 (4.5)              | 84 (32.1)                 | Reference |
| E. coli                              | 16 (36.4)            | 50 (19.1)                 | < 0.001 |
| Others                               | 26 (59.1)            | 128 (48.9)                | < 0.001 |
| Birth weight < 1,500 g               | 32 (72.7)            | 34 (12.9)                 | < 0.001 |
| Gestational age < 34 wk              | 36 (81.8)            | 75 (28.6)                 | < 0.001 |
| Male                                 | 28 (63.6)            | 144 (55.0)                | 0.28    |
| Cesarean delivery                    | 27 (61.4)            | 158 (60.3)                | 0.89    |
| Multiple gestation                   | 3 (6.8)              | 9 (3.4)                   | 0.72    |
| Membrane rupture ≥ 18 h before delivery | 19 (43.2)          | 93 (35.5)                 | 0.33    |
| Exposure to intrapartum antibiotics  | 18 (40.9)            | 76 (29.0)                 | < 0.01  |
| Prepregestational diabetes mellitus  | 7 (15.9)             | 31 (11.8)                 | 0.45    |
| Maternal intrapartum fever           | 9 (20.1)             | 48 (18.3)                 | 0.74    |

DISCUSSION

Despite several advancements in neonatal intensive care, EOS remains the most common cause of neonatal morbidity and mortality. However, few studies have investigated EOS in China. This retrospective study describes the epidemiology of EOS among the infants born in Suzhou, China, over a 7-year period.

In our study, the most frequent early-onset pathogens causing the infant infections were GBS and E. coli, which is consistent with the results from previous studies(8,10,11). Other pathogens were notably less frequent. Schrag et al. reported that viridans streptococci infections to be a risk factor for death(7). Further, a study conducted in Italy did not observe E. coli to be the most common pathogen associated with sepsis deaths (16/306, 5.2%). The results of the multivariate logistic regression analysis indicated that E. coli was significantly more likely to result in death than GBS. However, a study conducted in Italy did not observe E. coli infections to be a risk factor for death(7). Further, larger surveillance studies are required to determine whether E. coli infection is associated with a high risk of death in neonates in China.

Antibiotic resistance is a major public health threat (14–16), and, in our study, 54% of the GBS isolates were resistant to erythromycin and 33% to clindamycin. All of the E. coli isolates were resistant to levofloxacin. We do not have the necessary data to assess whether the high rate of resistance reflects either the antibiotic-resistant patterns in the neonatal intensive care units included in the present study or the antibiotic-resistant patterns in the genital flora of the mothers involved in our study. Furthermore, we do not have any information on antibiotic use during pregnancy prior to hospitalization of the mothers to deliver their infants.

In conclusion, GBS remains to be the most frequent pathogen that causes infection in infants. E. coli was the most common pathogen associated with neonatal mortality. Prevention of E. coli sepsis, specifically among preterm infants, remains to be a challenge.

**Conflict of interest** None to declare.

**REFERENCES**

1. McCracken GH, Jr. Group B streptococci: the new challenge in neonatal infections. J Pediatr. 1973;82:703-6.
2. Schuchat A, Zywicki SS, Dinsmoor MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics. 2000;105:21-6.
3. Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of...
early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. Pediatrics. 1999;103:678.

4. Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med. 2002;347:240-7.

5. Glikman D, Curiel N, Glatman-Freedman A, et al. Nationwide epidemiology of early-onset sepsis in Israel 2010-2015, time to re-evaluate empiric treatment. Acta Paediatr. 2019;108:2192-8.

6. Mendoza-Palomar N, Balasch-Carulla M, González-Dí Lauro S, et al. *Escherichia coli* early-onset sepsis: trends over two decades. Eur J Pediatr. 2017;176:1227-34.

7. Berardi A, Baroni L, Bacchi Reggiani ML, et al. The burden of early-onset sepsis in Emilia-Romagna (Italy): a 4-year, population-based study. J Matern Fetal Neonatal Med. 2016;29:3126-31.

8. Stoll BJ, Hansen NJ, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and *E. coli* disease continues. Pediatrics. 2011;127:817-26.

9. Sarff LD, Platt LH, McCracken GH, Jr. Cerebrospinal fluid evaluation in neonates: comparison of high-risk infants with and without meningitis. J Pediatr. 1976;88:473-7.

10. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014. Pediatrics. 2016;138:pii:e20162013.

11. Guan X, Mu X, Ji W, et al. Epidemiology of invasive group B streptococcal disease in infants from urban area of South China, 2011-2014. BMC Infect Dis. 2018;18:14.

12. Bauserman MS, Laughon MM, Hornik CP, et al. *Group B Streptococcus* and *Escherichia coli* infections in the intensive care nursery in the era of intrapartum antibiotic prophylaxis. Pediatr Infect Dis J. 2013;32:208-12.

13. Puopolo KM, Benitz WE, Zaoutis TE, et al. Management of Neonates Born at ≤34 6/7 Weeks’ Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics. 2018;142:e20182896.

14. Chamoun K, Farah M, Araj G, et al. Surveillance of antimicrobial resistance in Lebanese hospitals: retrospective nationwide compiled data. Int J Infect Dis. 2016;46:64-70.

15. Brinkac L, Voorhies A, Gomez A, et al. The Threat of Antimicrobial Resistance on the Human Microbiome. Microb Ecol. 2017;74:1001-8.

16. Cantón R, Horcajada JP, Oliver A, et al. Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. Enferm Infecc Microbiol Clin. 2013;31 Suppl 4:3-11.