Etiology, antimicrobial resistance, and risk factors of neonatal sepsis in China: a systematic review and meta-analysis from data of 30 years

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**ABSTRACT**

**Objective:** To evaluate the regional etiology, antimicrobial resistance (AMR) pattern, and risk factors in neonates with sepsis in China.

**Methods:** We performed a systematic review and meta-analysis by searching Medline, Embase, Scopus, and Web of Science in December 2020. Studies of neonatal sepsis from China published between 2011 and 2020 were included. We pooled the proportion of pathogens and calculated the odds ratios of risk factors with 95% CIs using a random-effects model.

**Results:** We included 29 studies of 164,750 neonates with sepsis. The studies comprise data from 1990 to 2019. Coagulase-negative staphylococci (CoNS), \textit{Escherichia coli} and \textit{Klebsiella} spp accounted for 33% (95% CI 24–43), 17% (13–20), and 14% (11–17), respectively. Group B streptococcus (GBS) was the predominant isolate in early-onset sepsis (EOS) (21%, 95% CI 10–31), while the proportion of CoNS was the largest in late-onset sepsis (LOS) (32%, 95% CI 22–43). Resistance of CoNS to penicillin was found in 95% (95% CI 92–98) of 511 cases and \textit{Klebsiella} spp to ampicillin in 95% (95% CI 90–99) of 364 cases. Maternal underlying diseases (2.61, 95% CI 1.48–4.61), mechanical ventilation (2.41, 1.37–4.23), central venous catheter placement (2.74, 1.77–4.26), peripherally inserted central catheter (PICC) placement (4.26, 2.80–6.49), multiple antibiotic uses (5.35, 1.85–15.43) and total parenteral nutrition (7.96, 2.04–31.02) were risk factors of neonatal sepsis.

**Conclusion:** CoNS, \textit{E. coli}, and \textit{Klebsiella} spp were the predominant pathogens in neonatal sepsis in China. AMR was still a significant issue in NICUs. Total parenteral nutrition, multiple antibiotic uses, and PICC placement were the most relevant risk factors.

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**Introduction**

Neonatal sepsis or meningitis was one of the leading causes of neonatal death [1]. The population-level estimate for neonatal sepsis was 2202 per 100,000 live births, with mortality between 11 and 19% [2]. In mainland China, the overall positivity of blood culture examination was 17.0% for neonatal patients with suspected sepsis during the first decade of the twenty-first century [3]. The difference was found in mortality and microbiological patterns among adult and pediatric patients with sepsis [3]. Broad-spectrum antibiotic drugs were widely used in neonates from China and only 24.2% of neonates received Access antibiotic use, according to a global report using the WHO Essential Medicines List Access, Watch, and Reserve (AWaRe) classification [4]. The antimicrobial resistance (AMR) patterns are becoming a significant issue with high rates of resistance in Gram-negative species and an increasing incidence of multidrug-resistant pathogens [5,6].

Previous publications described the distribution and AMR patterns in neonatal sepsis in different regions of China. Subsequent systematic reviews involved articles mostly published in the Chinese literature without proper quality assessment [3,7,8]. Recently, more studies published in the English literature with a higher quality of design from various provinces have emerged. Therefore, we conducted this systematic review to broadly observe the etiological distribution...
and AMR patterns, and to identify the risk factors of neonatal sepsis from China.

**Methods**

**Search strategy and selection criteria**

We performed this systematic review and meta-analysis in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations. A systematic search of Medline, Embase, Scopus, and Web of Science was conducted on 3 December 2020, to identify studies from China published from 1 January 2011, to the date of search. The following terms were used on Scopus in various combinations: “sepsis,” “septic,” “neonatal,” “newborn,” “infant,” “China,” “Chinese.” A similar strategy was used in the search of other databases (see Appendix 1). We restricted the language to English and the doc-type to article.

Two reviewers (YQY and XRH) screened the abstracts and titles after they were imported into Endnote and the duplicate records were removed. They assessed for relevance to the clinical studies of neonatal sepsis from China. After full-text articles were assessed, studies were excluded if they were studies from other countries or had no data accessible to etiology, AMR, or risk factors of neonatal sepsis. Case reports and studies focused on a single pathogen were excluded because they might lead to biased estimates of the results, especially the etiology of the pathogens and AMR. We defined sepsis as having positive culture results of bacteria or fungus from blood or cerebrospinal fluid samples. Therefore, studies without culture-proven neonatal sepsis were also excluded. Cases of sepsis with positive culture for coagulase-negative staphylococci (CoNS) were identified only if the clinical course was suggestive of sepsis and appropriate antibiotic therapy was given. Disagreements were resolved by discussion with a third reviewer (LJW).

**Quality assessment and data extraction**

We applied the Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) checklist to assess the quality of the observational studies [9]. Two reviewers (YQY and XRH) evaluated the studies independently. The checklist was firstly applied by Okomo et al. in neonates, and we improved the criteria by scores [10]. Each item reporting was classified with “not reported or unclear,” “some information mentioned but insufficient,” or “clear and detailed information provided,” scored as 0, 1, and 2, respectively. Studies with higher total scores had a better quality.

Three reviewers (YQY, XRH, and LJW) independently collected data from the studies included. Information was extracted by a pre-designed form, including study details (publication year, study year, study design, regions and locations, population), number of isolates of the pathogens and AMR, and risk factors of sepsis and mortality.

**Statistical analysis**

All analyses were pooled using the Dersimonian and Laird method in a random-effects model. We pooled the dichotomous non-comparative data for the etiology of the pathogens and AMR as proportions with 95% CI. We pooled the comparative dichotomous data for risk factors as odds ratios with 95% CI. Heterogeneity was reported as $I^2$ statistics. Subgroup analysis was undertaken mainly by regions. All statistical analyses were performed with Stata V.16.0 (StataCorp, College Station, TX, USA).

**Results**

**Characteristics of included studies**

Of 6419 citations searched initially, 29 eligible studies were included in this systematic review (Figure 1). The total population included 164,750 neonates. The data from the studies were retrieved between 1990 and 2019. Eight studies were from east China [11–18], one from northern China [19], nine from southern China [20–28], seven from west China [29–35], one from central and west China [36], one from southern and northern China [37], and two from all regions [38,39] (see Appendix 2). Besides two studies of 25 hospitals from 19 provinces [38,39], two multi-center studies involved data from different regions [36,37], one from the same region but different cities [31], and one from the same city [13]. There were two prospective cohort studies [11,37], 13 retrospective cohort studies [12,13,15,16,21,23,25,28,30,31,36,38,39], seven case-control studies [18,19,22,27,29,32,34], three cross-sectional studies [14,24,33] and the other four were case series [17,20,26,35]. All studies were hospital-based and from tertiary referral facilities or large national hospitals. Detailed characteristics of all included studies are given in Appendix 3.
Quality assessment

The average score for the studies evaluated using STROBE-NI criteria was 32 (range 23–40). 19 (66%) studies reported detailed information in study design, 9 (31%) in setting description, 25 (86%) in the eligibility criteria of participants, and 20 (69%) in the definition of variables. Only 5 (17%) studies had information of bias and 4 (14%) of study size. No information was found in addressing missing data and description of sensitivity analyses in all studies. The main results were clear and detailed in 27 (93%) studies. Because of retrospective designed in most studies, only 5 (17%) had a flow diagram or reported participation in detail. Sixteen (55%) studies gave a cautious overall interpretation of results. Limitations were not reported in 13 (45%) studies (see Appendix 4).
Table 1. Pooled regional distribution of pathogen in neonatal sepsis.

| All sepsis          | East China | Southern China | West China | Total*  |
|---------------------|------------|----------------|------------|---------|
|                     | n          | Proportion (95% CI) | n          | Proportion (95% CI) | n          | Proportion (95% CI) | n          | Proportion (95% CI) |
| Gram positives      | 396       | 0.63 (0.52–0.74) | 1266      | 0.56 (0.45–0.68) | 658       | 0.51 (0.39–0.62) | 2320      | 0.56 (0.50–0.63)   |
| CoNS                | 260       | 0.44 (0.21–0.67) | 656       | 0.30 (0.14–0.46) | 404       | 0.30 (0.20–0.40) | 1453      | 0.33 (0.24–0.43)   |
| S. aureus           | 21        | 0.03 (0.00–0.14) | 218       | 0.08 (0.05–0.11) | 76        | 0.05 (0.04–0.07) | 336       | 0.06 (0.04–0.07)   |
| Enterococcus spp    | 30        | 0.04 (0.01–0.06) | 104       | 0.05 (0.03–0.07) | 74        | 0.05 (0.03–0.08) | 208       | 0.05 (0.03–0.06)   |
| Listeria spp        | 5         | 0.01 (0.00–0.02) | 1         | 0.00 (0.00–0.01) | 37        | 0.04 (0.01–0.06) | 43        | 0.01 (0.00–0.02)   |
| Streptococcus spp   | 31        | 0.03 (0.01–0.07) | 54        | 0.03 (0.01–0.04) | 46        | 0.03 (0.00–0.03) | 142       | 0.03 (0.02–0.04)   |
| GBS                 | 55        | 0.29 (0.23–0.35) | 181       | 0.08 (0.05–0.12) | 54        | 0.01 (0.00–0.03) | 240       | 0.09 (0.05–0.13)   |
| Gram negatives      | 225       | 0.32 (0.21–0.43) | 1016      | 0.40 (0.29–0.50) | 509       | 0.48 (0.34–0.62) | 1750      | 0.40 (0.33–0.46)   |
| Klebsiella spp      | 49        | 0.07 (0.03–0.10) | 368       | 0.15 (0.10–0.20) | 198       | 0.16 (0.10–0.22) | 662       | 0.14 (0.11–0.17)   |
| E. coli             | 94        | 0.14 (0.03–0.26) | 371       | 0.16 (0.11–0.22) | 206       | 0.17 (0.10–0.24) | 760       | 0.17 (0.13–0.20)   |
| Enterobacter spp    | 9         | 0.01 (0.00–0.02) | 67        | 0.04 (0.03–0.05) | 42        | 0.03 (0.02–0.05) | 128       | 0.03 (0.02–0.04)   |
| Acinetobacter spp   | 2         | 0.00 (0.00–0.01) | 79        | 0.03 (0.02–0.05) | 28        | 0.03 (0.02–0.04) | 109       | 0.02 (0.01–0.03)   |
| Pseudomonas spp     | 18        | 0.05 (0.03–0.07) | 32        | 0.02 (0.01–0.04) | 37        | 0.02 (0.00–0.04) | 87        | 0.03 (0.01–0.04)   |
| Serratia spp        | 2         | 0.01 (0.00–0.02) | 23        | 0.03 (0.00–0.05) | 3         | 0.03 (0.01–0.07) | 28        | 0.02 (0.01–0.03)   |
| Fungus              | 39        | 0.07 (0.02–0.12) | 122       | 0.05 (0.04–0.06) | 39        | 0.03 (0.01–0.05) | 200       | 0.05 (0.04–0.06)   |
| Candida spp         | 26        | 0.05 (0.03–0.08) | 57        | 0.05 (0.03–0.06) | 2         | 0.02 (0.00–0.04) | 85        | 0.04 (0.03–0.05)   |

Controlled ES: early-onset sepsis; LOS: late-onset sepsis; CoNS: coagulase-negative staphylococci; GBS: group B streptococcus. *Including one study from central China, two from northern China and two from all regions. Distribution of GBS is excluded from Streptococcus spp and calculated separately. Distribution of E. coli is also excluded from Enterobacter spp and calculated separately.

Etiology

Pooled regional distribution of pathogens in total sepsis, EOS, and LOS were listed in Table 1. The most common isolates in neonatal sepsis included coagulase-negative staphylococci (CoNS) (33%, 95% CI 24–43), Escherichia coli (17%, 95% CI 13–20) and Klebsiella spp (14%, 95% CI 11–17). In EOS, group B streptococcus (GBS) was the predominant isolate (21%, 95% CI 10–31), while the proportion of CoNS was the largest in LOS (32%, 95% CI 22–43). The prevalence of E. coli bacteremia was higher in EOS, compared with LOS (19 vs. 13%). In contrast, the prevalence of Klebsiella spp bacteremia in LOS was more common (15 vs. 8%). Listeria spp accounted for 5% (95% CI 2–9) of cases in EOS. High intraregional heterogeneity was found in CoNS (I² range 80.42–99.09%). We also observed significant differences in the distribution of pathogens inter-regionally (see Appendix 5). In particular, GBS in neonatal sepsis was reported more common in east China (29%, 95% CI 23–35), than in southern and west China (8%, 95% CI 5–12; 1%, 95% CI 0–3).

Antimicrobial resistance

Resistance to the most common isolates in Gram-positive and Gram-negative bacterial neonatal sepsis was
Table 2. Pooled antimicrobial resistance in Gram-positive bacterial neonatal sepsis.

| CoNS | Number of tested | Resistance (95% CI) | Number of tested | Resistance (95% CI) |
|------|------------------|----------------------|------------------|----------------------|
| Penicillin | 511 | 95% (92–98) | 58 | 90% (82–98) |
| Oxacillin | 650 | 76% (69–83) | 92 | 31% (11–50) |
| Gentamicin | 742 | 39% (30–49) | 45 | 26% (2–50) |
| Clindamycin | 367 | 46% (41–51) | 84 | 42% (31–53) |
| Ciprofloxacin | 412 | 39% (28–50) | 42 | 11% (1–21) |
| Levofloxacin | 471 | 39% (32–46) | 46 | 11% (2–21) |
| Trimethoprim-sulfamethoxazole | 516 | 51% (41–61) | 96 | 13% (4–23) |

Table 3. Pooled antimicrobial resistance in Gram-negative bacterial neonatal sepsis.

| Klebsiella spp | Number of tested | Resistance (95% CI) | E. coli | Number of tested | Resistance (95% CI) |
|---------------|------------------|----------------------|---------|------------------|----------------------|
| Ampicillin | 364 | 95% (90–99) | 478 | 78% (72–84) |
| Ampicillin/sulbactam | 243 | 78% (61–96) | 269 | 48% (21–75) |
| Piperacillin-Tazobactam | 340 | 38% (19–57) | 319 | 8% (2–14) |
| Ceftazidime | 471 | 58% (31–84) | 504 | 32% (16–48) |
| Ceftriaxone | 160 | 72% (51–92) | 249 | 49% (31–66) |
| Cefepime | 372 | 46% (25–68) | 455 | 21% (10–32) |

Presented in Tables 2, 3. Higher resistance to the commonly used antibiotics was found in CoNS and Klebsiella spp (mostly K. pneumoniae), compared with Staphylococcus aureus and E. coli, respectively. Resistance to β-lactam antibiotics was significantly high in CoNS (95% to penicillin, 95% CI 92–98) and Klebsiella spp (95% to ampicillin, 95% CI 90–99). Fortunately, the resistance to ampicillin/sulbactam and piperacillin-tazobactam in Klebsiella spp was lower (78 and 38%, respectively) (see Appendix 6). Extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria were reported to have high resistance to third-generation cephalosporins [14,22]. Resistance of CoNS to vancomycin was only reported in two studies [12,33]. However, resistance to carbapenem antibiotics was reported in 5 of 8 studies in Klebsiella spp [12,15,17,24,31,33,35,36] and in 1 of 9 studies in E. coli [12,13,15,17,24,31,33,35,36].

Risk factors

Compared with neonates without sepsis, the odds of maternal underlying diseases (2.61, 95% CI 1.48–4.61), mechanical ventilation (2.41, 1.37–4.23), central venous catheter placement (2.74, 1.77–4.26), peripherally inserted central catheter (PICC) placement (4.26, 2.80–6.49), multiple antibiotic use (5.35, 1.85–15.43), and total parenteral nutrition (7.96, 2.04–31.02) were higher in those with sepsis. Maternal vaginal delivery (0.86, 0.56–1.34) and neonatal steroid use (1.25, 0.77–2.05) were irrelevant to neonatal sepsis (Figure 2). Xiao et al. [28] also found that postnatal age and parity were independent risk factors of neonatal sepsis (1.176 and 0.692, respectively, p < .001). Risk factors of death associated with neonatal sepsis include birth weight <1500 g (7.81, 2.49–24.43) and neonatal respiratory distress (16.30, 1.91–139.36). However, no differences were observed in other characteristics (Figure 3). Some of the included studies reported invasive fungal infection only, especially candidemia [18,19,29,30,32,34].

Discussion

This systematic review identified 29 studies (164,750 neonates) published between 2011 and 2020. Our study described the distribution of pathogens in different regions, the AMR to common pathogens, and risk factors of sepsis and death in neonates in China from data between 1990 and 2019.

Li et al. [7] performed a meta-analysis of neonatal sepsis in China in 2018 including Chinese literature from 2009 to 2014. The proportion of Staphylococcus was far larger than other isolates. Another review of Chinese literature from 2016 to 2018 showed that CoNS accounted for 66.12% in Gram-positive neonatal sepsis, and Klebsiella spp and E. coli accounted for 41.64 and 34.78% in Gram-negative neonatal sepsis, respectively [40]. A meta-analysis of microbiological patterns in neonatal and pediatric patients from different regions of China showed no significant geographical differences in the proportion of pathogens [3]. However, our report firstly performed a meta-analysis of the specific distribution of pathogens from different regions of China in EOS and LOS. We discovered that GBS was the leading cause followed by CoNS and E. coli in EOS. Similarly, the reports from the UK and the US found GBS and E. coli were the most frequently
### Heterogeneity:

| Factor                          | Case          | Control       | Odds Ratio with 95% CI | Weight (%) |
|--------------------------------|---------------|---------------|------------------------|------------|
| **Central venous catheter**    |               |               |                        |            |
| Wang S (2017)                  | 164           | 40            | 9,843                  | 8,022      | 3.34 (2.36, 4.73) | 4.81 |
| Wang S (2017)                  | 218           | 108           | 10,643                 | 14,108     | 2.68 (2.12, 3.37) | 5.00 |
| Liu M (2015)                   | 16            | 3             | 2                      | 19         | 50.67 (7.51, 341.74) | 1.56 |
| Chen J (2016)                  | 40            | 29            | 24                     | 45         | 2.59 (1.30, 5.15)  | 3.98 |
| Fu J (2018)                    | 15            | 13            | 13                     | 7          | 0.62 (0.19, 2.02)  | 2.74 |
| Fu J (2016)                    | 28            | 20            | 18                     | 30         | 2.33 (1.03, 5.29)  | 3.63 |
| Heterogeneity: $\theta^2 = 0.16$, $I^2 = 69.63\%$, $H^2 = 3.29$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(3) = 15.46, p = 0.01$ |               |               |                        |            |
| **Maternal underlying diseases**|               |               |                        |            |
| Chen J (2016)                  | 31            | 38            | 19                     | 50         | 2.15 (1.06, 4.37)  | 3.92 |
| Fu J (2016)                    | 25            | 13            | 13                     | 25         | 3.70 (1.43, 9.54)  | 3.29 |
| Heterogeneity: $\theta^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(1) = 0.81$, $p = 0.37$ |               |               |                        |            |
| **Mechanical ventilation**     |               |               |                        |            |
| Wang S (2017)                  | 82            | 122           | 3,384                  | 14,481     | 2.88 (2.17, 3.81)  | 4.93 |
| Wang S (2017)                  | 91            | 235           | 6,064                  | 18,687     | 1.19 (0.94, 1.52)  | 4.99 |
| Chen J (2016)                  | 43            | 26            | 28                     | 41         | 2.42 (1.22, 4.80)  | 3.99 |
| Fu J (2018)                    | 24            | 4             | 10                     | 10         | 6.00 (1.52, 23.71) | 2.35 |
| Fu J (2016)                    | 34            | 14            | 21                     | 27         | 3.12 (1.34, 7.26)  | 3.56 |
| Heterogeneity: $\theta^2 = 0.29$, $I^2 = 85.02\%$, $H^2 = 6.68$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(4) = 26.70$, $p = 0.00$ |               |               |                        |            |
| **Multiple antibiotic use**    |               |               |                        |            |
| Liu M (2015)                   | 11            | 8             | 2                      | 19         | 13.06 (2.34, 72.82) | 1.80 |
| Chen J (2016)                  | 37            | 32            | 9                      | 60         | 7.71 (3.31, 17.95) | 3.56 |
| Fu J (2018)                    | 18            | 10            | 13                     | 7          | 0.97 (0.29, 3.22)  | 2.70 |
| Fu J (2016)                    | 31            | 17            | 8                      | 40         | 9.12 (3.48, 23.87) | 3.26 |
| Heterogeneity: $\theta^2 = 0.81$, $I^2 = 71.86\%$, $H^2 = 3.55$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(3) = 10.66$, $p = 0.01$ |               |               |                        |            |
| **Neonatal steroid use**       |               |               |                        |            |
| Yu Y (2013)                    | 4             | 41            | 6                      | 84         | 1.37 (0.37, 5.11)  | 2.45 |
| Fu J (2016)                    | 12            | 36            | 7                      | 41         | 1.95 (0.69, 5.49)  | 3.08 |
| Kung YH (2013)                 | 24            | 140           | 23                     | 141        | 1.05 (0.57, 1.95)  | 4.16 |
| Heterogeneity: $\theta^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(2) = 1.03$, $p = 0.60$ |               |               |                        |            |
| **PICC**                       |               |               |                        |            |
| Yu Y (2013)                    | 28            | 17            | 22                     | 68         | 5.09 (2.36, 11.00) | 3.75 |
| Kung YH (2013)                 | 134           | 30            | 87                     | 77         | 3.95 (2.40, 6.52)  | 4.46 |
| Heterogeneity: $\theta^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(1) = 0.29$, $p = 0.59$ |               |               |                        |            |
| **Total parenteral nutrition** |               |               |                        |            |
| Chen J (2016)                  | 58            | 11            | 23                     | 46         | 10.55 (4.66, 23.85) | 3.63 |
| Fu J (2018)                    | 26            | 2             | 19                     | 1          | 0.68 (0.06, 8.11)  | 1.06 |
| Fu J (2016)                    | 45            | 3             | 20                     | 28         | 21.00 (5.71, 77.21) | 2.49 |
| Heterogeneity: $\theta^2 = 0.90$, $I^2 = 65.36\%$, $H^2 = 2.89$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(2) = 5.77$, $p = 0.06$ |               |               |                        |            |
| **Vaginal delivery**           |               |               |                        |            |
| Chen J (2016)                  | 28            | 41            | 33                     | 36         | 0.75 (0.38, 1.46)  | 4.01 |
| Fu J (2018)                    | 13            | 15            | 7                      | 13         | 1.61 (0.49, 5.25)  | 2.74 |
| Fu J (2016)                    | 28            | 20            | 24                     | 24         | 1.40 (0.63, 3.13)  | 3.66 |
| Xiao T (2017)                  | 112           | 80            | 74                     | 32         | 0.61 (0.37, 1.00)  | 4.45 |
| Heterogeneity: $\theta^2 = 0.07$, $I^2 = 31.95\%$, $H^2 = 1.47$ |               |               |                        |            |
| Test of $\theta_i = \theta_j$: $Q(3) = 4.41$, $p = 0.22$ |               |               |                        |            |

Figure 2. Risk factors associated with neonatal sepsis. Two studies were involved in Wang et al. [36]. PICC: peripherally inserted central catheter.
isolated pathogens in EOS [41–44]. Huang et al. [45] illustrated the distribution of the maternal GBS colonization in mainland China, and Fujian and Guangdong provinces in southern China had the highest rate of colonization. We also found that the distribution of GBS infection in EOS was significantly higher in east and southern China. GBS had the highest incidence (0.30 per 1000 live births) in EOS in a retrospective study from 2012 to 2016 in southern China, similar to the results from the UK [24,41]. From 2006 to 2015, due to intrapartum antibiotic prophylaxis (IAP), early-onset GBS disease incidence declined significantly from 0.37 to 0.23 per 1000 live births (p < .001) in the US [46]. Therefore, it is necessary to highlight the importance of GBS screening of pregnant women and IAP especially in regions with high maternal GBS colonization rates of China.

Furthermore, we found that CoNS, Klebsiella spp, and E. coli were the predominant isolates in LOS. It was reported that K. pneumoniae and A. baumannii were the most frequently identified organisms causing nosocomial pneumonia, whereas CoNS was the most common pathogen causing nosocomial bloodstream infection in China [47,48]. A prospective study from Taiwan showed a high prevalence of nosocomial infections (17.5%) between 2004 and 2005, including central intravascular catheter-associated bloodstream infection (13.7%), total parenteral nutrition (TPN)-associated bloodstream infection (15.8%), and ventilator-associated pneumonia (18.6%) [49]. More efforts

Figure 3. Risk factors of death in neonatal sepsis.
should be taken to perform quality improvement in hospitalization and the use of life-sustaining medical devices in NICUs.

Our results of AMR patterns were under the studies from Li et al. and Zhang et al. [7,8]. Also, the proportion of Gram-negative cultures resistant to third-generation cephalosporins was as high as the data from the NeoAMR network [5]. Zhu et al. [14] found that resistance of ESBL-producing multi-drug resistant E. coli to third-generation cephalosporins increased from 2002 to 2018. In general, initial empirical treatment of early-onset bacterial infections includes ampicillin plus aminoglycoside, with a third-generation cephalosporin or carbapenem for meningitis. In LOS, initial empirical treatment consists of vancomycin plus aminoglycoside, and cephalosporin if meningitis is suspected [50]. Aminoglycosides have rarely been used in children in China due to ototoxicity since 2000 [33]. More awareness should be raised on the increasing high resistance to third-generation or fourth-generation cephalosporins in Gram-negative organisms. The Surveillance and Correction of Unnecessary Antibiotic Therapy (SCOUT) study reduced antibiotic use in a level 3 NICU from the US and presented the feasibility in optimizing antibiotic stewardship strategies [51]. A program called Smart Use of Antibiotics Program (SMAP) also showed effectiveness in reducing antibiotic exposure in a NICU in Shanghai, China [52]. Further work is required to reduce AMR infection in NICUs in China and worldwide.

Risk factors of neonatal sepsis were less reported in studies from China. In 2014, the Kaiser Permanente Division of Research developed a neonatal EOS risk calculator in newborns ≥34 weeks’ gestation [53]. The use of EOS calculators has increased worldwide. Recent studies proved that the implementation reduces the need for diagnostic testing and empirical antibiotic treatment for suspected EOS substantially [54,55]. However, the application in non-Western countries, especially with different health care settings, needs further exploration.

The strengths of this study are the wide description of the characteristics of neonatal sepsis in China and the rigorous quality assessment of the included studies. However, there are some limitations remain. Firstly, high heterogeneity was found in the distribution of isolates and drug resistance. Characteristics of sepsis were different in hospitals intra-regionally and inter-regionally. Secondly, the literature search only included articles published in the last 10 years and the language was restricted to English, which may result in a risk of bias.

Our meta-analysis was based on the data of 30 years, therefore, the changing trends of the characteristics may lead to high heterogeneity. Characteristics of 4 studies including data of different periods were listed in Appendix 7. The AMR to gentamicin was declined, and the AMR to ampicillin and piperacillin-tazobactam increased in the last 30 years. Lu et al. [33] presented the trends of pathogens and AMR profiles in southwest China from 1990 to 2014. The occurrence rates of pathogens remained stable during the study period. A recent study from Suzhou, China also found a significant reduction in CoNS and K. pneumoniae, and a reduced sensitivity against the first- and second-generation antibiotics in the last decade [56]. Care bundles were applied in different countries these years, including China [57]. Meta-analysis revealed a statistically significant reduction in central line-associated bloodstream infections (CLABSI) following the introduction of care bundles (RR 0.40, \( p < .00001 \)) [58]. From 2015, a national group named Neonatal Intensive Care Units using the Evidence-based Practice for Improving Quality study (REIN-EPIQ Study Group) of twenty-five tertiary hospitals from 19 provinces in China has been established. The efforts in quality improvement in NICUs may be beneficial to reduce neonatal infection in the future.

Conclusions

In conclusion, our study was the first study to broadly describe the characteristics of neonatal sepsis in China with a high-quality assessment of publications. We expect our research could provide more evidence for informing guidelines and better clinical care of neonatal sepsis in different regions of China. The results may be recommended as comparisons with studies carried out in other countries and as implications for global practice in the treatment and prevention of neonatal sepsis.

Disclosure statement

The authors report no conflict of interest.

Author contributions

YQY designed the study and drafted the initial manuscript. YQY, XRH, and LJW collected the data. YQY, XRH, and YHY analyzed the data. All authors reviewed and revised the manuscript. PYC contributed to the concept, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.
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Data availability statement
All data relevant to the study are included in the article or uploaded as supplementary information. Data are available from the corresponding author.

References
[1] Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151–2161.
[2] Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018;6(3):223–230.
[3] Chen XC, Yang YF, Wang R, et al. Epidemiology and microbiology of sepsis in mainland China in the first decade of the 21st century. Int J Infect Dis. 2015;31:9–14.
[4] Hsia Y, Lee BR, Versporten A, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Health. 2019;7(7):e861–e871.
[5] Li G, Bielicki JA, Ahmed A, et al. Towards understanding global patterns of antimicrobial use and resistance in neonatal sepsis: insights from the NeoAMR network. Arch Dis Child. 2020;105(1):26–31.
[6] Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100(3):F257–F263.
[7] Li JY, Chen SQ, Yan YY, et al. Identification and antimicrobial resistance of pathogens in neonatal sepsis in Suzhou. BMC Pediatr. 2020;20(1):261.
[8] Yuan T, Dong H, Cao H, Zheng H. Pathogenic bacteria distributions and drug resistance analysis in 96 cases of neonatal sepsis. BMC Pediatr. 2017;17(1):44.
[9] Yu Y, Du L, Yuan T, et al. Risk factors and clinical analysis for invasive fungal infection in neonatal intensive care unit patients. Amer J Perinatol. 2012;30(07):589–594.
[10] Liu M, Huang S, Guo L, et al. Clinical features and risk factors for blood stream infections of Candida in neonates. Exp Ther Med. 2015;10(3):1139–1144.
[11] Li Y, Xiao Z, Li Z, et al. 116 cases of neonatal early-onset or late-onset sepsis: a single center retrospective analysis on pathogenic bacteria species distribution and antimicrobial susceptibility. Int J Clin Exp Med. 2013;6(8):693–699.
[12] Chen IL, Chiu NC, Chi H, et al. Changing of bloodstream infections in a medical center neonatal intensive care unit. J Microbiol Immunol Infect. 2017;50(4):514–520.
[13] Tsai MH, Lee IT, Chu SM, et al. Clinical and molecular characteristics of neonatal extended-spectrum β-lactamase-producing gram-negative bacteremia: a 12-year case-control-control study of a referral center in Taiwan. PLOS One. 2016;11(8):e0159744.
[14] Guo J, Luo Y, Wu Y, et al. Clinical characteristic and pathogen spectrum of neonatal sepsis in Guangzhou city from June 2011 to June 2017. Med Sci Monit. 2019;25:2296–2304.
[15] Gao K, Fu J, Guan X, et al. Incidence, bacterial profiles, and antimicrobial resistance of culture-proven neonatal sepsis in South China. Infect Drug Resist. 2019;12:3797–3805.
[16] Tsai MH, Lee CW, Chu SM, et al. Infectious complications and morbidities after neonatal bloodstream infections: an observational cohort study. Medicine. 2016;95(11):e3078.
[17] Lim WH, Lien R, Huang YC, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediatr Neonatol. 2012;53(4):228–234.
[27] Kung YH, Hsieh YF, Weng YH, et al. Risk factors of late-onset neonatal sepsis in Taiwan: a matched case-control study. J Microbiol Immunol Infect. 2016;49(3):430–435.

[28] Xiao T, Chen LP, Liu H, et al. The analysis of etiology and risk factors for 192 cases of neonatal sepsis. Biomed Res Int. 2017;2017:1–6.

[29] Chen J, Jiang Y, Wei B, et al. Epidemiology of and risk factors for neonatal candidemia at a tertiary care hospital in western China. BMC Infect Dis. 2016;16(1):700.

[30] Zeng Z, Tian G, Ding Y, et al. Epidemiology, antifungal susceptibility, risk factors and mortality of invasive candidiasis in neonates and children in a tertiary teaching hospital in Southwest China. Mycoses. 2020;63(11):1164–1174.

[31] Zhao Z, Yu JL, Zhang HB, et al. Five-year multicenter study of clinical tests of neonatal purulent meningitis. Clin Pediatr. 2018;57(4):389–397.

[32] Fu J, Ding Y, Jiang Y, et al. Persistent candidemia in very low birth weight neonates: risk factors and clinical significance. BMC Infect Dis. 2018;18(1):558.

[33] Lu Q, Zhou M, Tu Y, et al. Pathogen and antimicrobial resistance profiles of culture-proven neonatal sepsis in Southwest China, 1990–2014. J Paediatr Child Health. 2016;52(10):939–943.

[34] Fu J, Wang X, Wei B, et al. Risk factors and clinical analysis of candidemia in very-low-birth-weight neonates. Am J Infect Control. 2016;44(11):1321–1325.

[35] Jiang Y, Kuang L, Wang H, et al. The clinical characteristics of neonatal sepsis infection in Southwest China. Intern Med. 2016;55(6):597–603.

[36] Wang S, Chen S, Feng W, et al. Clinical characteristics of nosocomial bloodstream infections in neonates in two hospitals, China. J Trop Pediatr. 2018;64(3):231–236.

[37] Al-Taiaar A, Hammoud MS, Cuqing L, et al. Neonatal infections in China, Malaysia, Hong Kong and Thailand. Arch Dis Child Fetal Neonatal Ed. 2013;98(3):F249–F255.

[38] Jiang S, Hong L, Gai J, et al. Early-onset sepsis among preterm neonates in China, 2015 to 2018. Pediatr Infect Dis J. 2019;38(12):1236–1241.

[39] Jiang S, Yang C, Yang C, et al. Epidemiology and microbiology of late-onset sepsis among preterm infants in China, 2015–2018: a cohort study. Int J Infect Dis. 2020;96:1–9.

[40] Wang J, Zhang H, Yan J, et al. Literature review on the distribution characteristics and antimicrobial resistance of bacterial pathogens in neonatal sepsis. J Matern Fetal Neonatal Med. 2020;1–10.

[41] Cailes B, Kortsaloudaki C, Bretty J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F547–F553.

[42] Schrag SJ, Farley MM, Petit S, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics. 2016;138(6).e20162013.

[43] Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011;127(5):817–826.

[44] Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the rise of Escherichia coli, and the need for novel prevention strategies. JAMA Pediatr. 2020;174(7):e200593.

[45] Huang J, Lin XZ, Zhu Y, et al. Epidemiology of group B streptococcal infection in pregnant women and diseased infants in mainland China. Pediatr Neonatol. 2019;60(5):487–495.

[46] Nanduri SA, Petit S, Smelser C, et al. Epidemiology of invasive early-onset and late-onset group B streptococcal disease in the United States, 2006 to 2015: multistate laboratory and population-based surveillance. JAMA Pediatr. 2019;173(3):224–233.

[47] Xu XF, Ma XL, Chen Z, et al. Clinical characteristics of nosocomial infections in neonatal intensive care unit in eastern China. J Perinat Med. 2010;38(4):431–437.

[48] Hei MY, Zhang XC, Gao XY, et al. Catheter-related infection and pathogens of umbilical venous catheterization in a neonatal intensive care unit in China. Am J Perinatol. 2012;29(02):107–114.

[49] Su BH, Hsieh HY, Chiu HY, et al. Nosocomial infection in a neonatal intensive care unit: a prospective study in Taiwan. Am J Infect Control. 2007;35(3):190–195.

[50] Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390(10104):1770–1780.

[51] Cantey JB, Wozniak PS, Pruszynski JE, et al. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis. 2016;16(10):1178–1184.

[52] Lu C, Liu Q, Yuan H, et al. Implementation of the smart use of antibiotics program to reduce unnecessary antibiotic use in a neonatal ICU: a prospective interrupted time-series study in a developing country. Crit Care Med. 2019;47(1):e1–e7.

[53] Escobar GJ, Puopolo KM, Wi S, et al. Stratification of risk of early-onset sepsis in newborns ≥34 weeks' gestation. Pediatrics. 2014;133(1):30–36.

[54] Achten NB, Klingenberg C, Benitz WE, et al. Association of use of the neonatal early-onset sepsis calculator with reduction in antibiotic therapy and safety: a systematic review and meta-analysis. JAMA Pediatr. 2019;173(11):1032–1040.

[55] Benitz WE, Achten NB. Technical assessment of the neonatal early-onset sepsis risk calculator. Lancet Infect Dis. 2021;21(5):e134–e140.

[56] Tang XJ, Sun B, Ding X, et al. Changing trends in the bacteriological profiles and antibiotic susceptibility in neonatal sepsis at a tertiary children's hospital of China. Transl Pediatr. 2020;9(6):734–742.

[57] Zhou Q, Lee SK, Hu XJ, et al. Successful reduction in central line-associated bloodstream infections in a Chinese neonatal intensive care unit. Am J Infect Control. 2015;43(3):275–279.

[58] Payne V, Hall M, Prieto J, et al. Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2018;103(5):F422–F429.