Clinical Characteristic and Pathogen Spectrum of Neonatal Sepsis in Guangzhou City from June 2011 to June 2017

Authors' Contribution:
- Junfei Guo*   
- Yasha Luo*   
- Yongbing Wu   
- Weiming Lai   
- Xiaoping Mu

* Junfei Guo and Yasha Luo contribute equally to the paper

Corresponding Authors:
- Junfei Guo, e-mail: gjunfei@sina.com
- Xiaoping Mu, e-mail: muxiaoping710@126.com

Source of support: Departmental sources

Background: Preterm and low birth weight (birth weight <2500 g) neonates are vulnerable to sepsis, and the causative pathogens vary in different regions and times. The objective of this study was to identify common organisms leading to neonatal sepsis and identify the characteristic of patients infected with different bacteria, which may help in the selection of antibiotics for empirical treatment.

Material/Methods: We retrospectively collected the clinical and microbiological data of neonates with culture-proven sepsis in our clinical setting from June 2011 to June 2017. The demography, composition, and distribution of the pathogens and the clinical characteristic of the cases infected with different bacteria were analyzed.

Results: Of a total of 1048 bacteria that were isolated from patient samples, detailed clinical and microbiological data of 297 cases were available. Escherichia coli, Klebsiella pneumoniae, and coagulase-negative Staphylococcus (co-NS) were the top 3 isolated pathogens. Streptococcus agalactiae predominantly led to early-onset sepsis, while K. pneumoniae and Staphylococcus aureus mainly led to late-onset sepsis. K. pneumoniae was mainly acquired in the hospital. Leukopenia was more commonly seen than leukocytosis in our study, and patients infected with K. pneumoniae and Candida spp encountered more thrombocytopenia.

Conclusions: The results of our study revealed the composition of the pathogens of neonatal sepsis in our region and the clinical characteristic of sepsis caused by different bacteria; these data may help in the selection of antibiotics for empirical treatment of neonates with high risk of sepsis.

MeSH Keywords: Infant, Newborn • Premature Birth • Sepsis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912375
Background

Neonatal sepsis is defined as a systemic infection with bacteria, virus, or fungus with/without signs and symptoms of infection in the first 4-weeks of life (<28 days) [1,2]. Although great improvements have been made in preventing and treating neonatal septicemia, it remains one of the most severe threats to the health of neonates, especially in developing countries. The prevalence of neonatal sepsis varies in different countries; in developed countries it is 1 to 10 cases per 1000 live births and in developing countries the incidence of neonatal septicemia increases to 49 to 170 cases per 1000 live births [3–5]. Depending on the time of onset, sepsis can be classified as early-onset sepsis or late-onset sepsis. Early-onset sepsis is defined as sepsis onset within 72 hours postnatal. Late-onset sepsis is sepsis happening more than 72 hours but no more than 28 days postnatal. The distinction has clinical relevance, as early-onset neonatal sepsis may be acquired before or during delivery while late-onset neonatal sepsis is mainly due to bacteria acquired from the hospital or community environment [1,6,7]. The pathogens of early-onset and late-onset neonatal sepsis are different. Escherichia coli and Streptococcus agalactiae are the most common organisms associated with early-onset neonatal sepsis; coagulase-negative Staphylococcus (co-NS) is the main pathogen of late-onset neonatal sepsis [6,8,9]. The spectrum of pathogens of neonatal sepsis varies among different settings and may change over time in the same setting [10–13].

Empirical antibiotic treatment is standard practice for neonates with high risk of sepsis, such as preterm labored infants, neonates born with premature rupture of membranes (PROM), and low birth weight (1501–2500 g) neonates or very low birth weight (<1500 g) neonates [14–16]. The diversity of organisms causing sepsis varies in different regions and changes over time even in the same location, which makes the choice of antibiotics for empirical treatment challenging. In addition, early exposure or prolonged exposure to antibiotics may lead to poor prognosis for the neonate [17].

As far as we know, there is no nationwide survey about the composition of the pathogens of neonatal sepsis in China. Two studies conducted in east and southwest of China revealed different pathogen spectrums causing neonatal septicemia. Studies in eastern China found that Staphylococcus aureus, K. pneumoniae, and Acinetobacter baumannii were the top 3 pathogens of neonatal sepsis, whereas studies in southwestern China revealed that co-NS, E. coli and K. pneumoniae were the top 3 pathogens [11,13]. The situation of neonatal sepsis in southern China is still unclear.

In the study presented here, we collected the clinical and microbiological data of neonates with blood culture proven bacteria sepsis in Guangdong women and children hospital, which is the main women and children healthcare center in south of China, located in Guangzhou City. We performed an analysis of the composition of pathogens and the distribution of pathogens among neonates with different clinical characteristics. We further analyzed the clinical characteristic of neonates infected with different bacteria, and the relationship of the time of hospitalized before a positive bacterial blood culture and the pathogens that lead to neonatal sepsis.

Material and Methods

Patients and population

This is a retrospective study aimed at addressing the composition of the pathogens and the clinical characteristics of neonatal sepsis in our clinical setting, which is a tertiary women and children care center in Guangzhou city in south China. This study was approved by the Ethics Committee of Guangdong Women and Children Hospital. The microbiological data of 1048 neonates with positive bacterial blood cultures during June 2011 and June 2017 were collected. Detail hospitalization data, clinical characteristics of 327 neonates, and the obstetric records of their mothers were collected. The inclusion criteria were as followed: 1) infants younger than 28 days post-partum; 2) with positive blood culture for bacteria; and 3) neonatal clinical data and mother’s obstetric data could be accessed. Those with only 1 positive blood culture for co-NS without any symptoms of sepsis were excluded due to the possibility of contamination during sample handling.

Data collection and analysis

We collected the following data: the isolated species of the pathogen, the age of neonates at admission, positive blood culture for bacteria results, gestational age (GA), delivery mode, born body weight, the incidence of premature rupture of membranes (PROM) and intrauterine fetal distress (IFD), total leukocytes count (TLC), platelet count, hemoglobin (Hb) concentration, plateletcrit (PCT) and hs-CRP level at the time of the positive blood culture. The interval between admission and positive blood culture was calculated to try to explain whether the infection was a hospital-acquired infection or not. Data analysis was performed using Microsoft Excel 2010; the data are presented as frequencies. Chi-square test was performed to analysis the distribution of pathogens. To access the risk factors associated with infection with different pathogens, univariate and multivariate analysis were performed. Kruskal-Wallis and Mann-Whitney U tests were performed for continuous data in univariate analyses. The χ² test and Fisher exact test were performed for dichotomous data in univariate analyses. P value <0.05 was considered statistically significant.
significant. Multivariate analyses were performed separately by using logistic regression to analyze the risk factors of morbidity in preterm infants. Gender, gestation week, delivery mode, and birth weight were included in the analysis. P<0.05 was considered statistically significant.

Results

Demography of patients

From June 2011 to June 2017, there were 1048 neonates who had a history of positive blood culture for bacteria in our hospital; detailed microbiological and clinical data of 327 patients were collected. Thirty-five cases were excluded due to only one positive blood culture, and the contamination rate was 10.7%. The details of the demographics of the study patients can be seen in Table 1.

Bacteria spectrum of neonatal sepsis

Among 1048 isolated pathogens, 432 (41%) were co-NS, 206 (20%) were E. coli, 126 (12%) were K. pneumoniae, 53 (5%) were Enterococcus spp, 52 (4.9%) were S. agalactiae, 47 (4.6%) were S. aureus, 34 (3.3%) were Candida spp, and 18 (1.7%) were A. baumannii. These bacteria were ranked the top 8 isolated pathogens of neonatal sepsis from June 2011 to June 2017 in our hospital (Figure 1A). Other bacteria accounted for 7.6% of all the isolates. The distribution of the pathogens of 297 neonates with detailed microbiology and clinical data were similar, except that E. coli was the most commonly seen pathogen among this population, followed by K. pneumoniae, and co-NS ranked the third most commonly seen bacteria (Figure 1B).

Bacteria composition of neonatal sepsis with different clinical characteristic

In this study, 188 and 109 bacteria were isolated from male and female neonates, respectively, and the distribution of the pathogens varied among male and female infants (χ²/IP, 17.87/0.0126) (Table 2). E. coli (26%), K. pneumoniae (24%), co-NS (15%), and Enterococcus spp (12%) ranked as the top 4 isolated pathogens among male neonates, and E. coli (26%), K. pneumoniae (21%), S. agalactiae (18%), and co-NS (16%) were the most commonly seen pathogens in female infants (Table 2). The difference in the distributions of the pathogens was greater among preterm and term infants (χ²/IP, 42.96/<0.0001) (Table 2). For those infants with GA <37 weeks, K. pneumoniae (31%), E. coli (25%), and Enterococcus spp (13%) were the top 3 isolated pathogens, and for those with GA ≥37 weeks, E. coli (26%), co-NS (24%), and S. agalactiae (18%) were the most common (Table 2). Composition of the isolated bacteria varied between vaginal delivery and caesarian section (χ²/IP, 23.82/<0.0012). E. coli (32%), K. pneumoniae (18%), co-NS (17%), and S. agalactiae (10%) were commonly seen in vaginally delivered infants, and K. pneumoniae (30%), E. coli (16%), Enterococcus spp (16%), and co-NS (13%) were the top 4 isolated pathogens in infants delivered by caesarian section (Table 2). In those infants whose mothers experienced PROM, E. coli (35%), K. pneumoniae (22%), and Enterococcus spp (14%) ranked as the top 3 isolated pathogens (Table 2). K. pneumoniae (26%), E. coli (19%), and co-NS (19%) were the top 3 isolated bacteria in neonates encountering intrauterine fetal distress (IFD) (Table 2). The composition of the pathogens was significantly different between early-onset sepsis and late-onset sepsis (χ²/IP, 62.75/<0.0001). For infants with early-onset sepsis, E. coli (32%) was the most commonly seen pathogen, followed by S. agalactiae (27%) and co-NS (17%), and for those with late-onset sepsis, K. pneumoniae (29%) was the most commonly seen pathogen followed by E. coli (23%).

Table 1. Demographics of patients.

| Characteristics | No. (%) (N=297) |
|-----------------|----------------|
| Maternal data   |               |
| Gestational age |               |
| Preterm (<37 weeks) | 165 (55%) |
| Term (≥37 weeks)  | 132 (45%) |
| Mode of delivery |               |
| Vaginal         | 177 (59%) |
| Caesarian section | 120 (41%) |
| PROM            | 81 (27%) |
| Intrauterine distress | 27 (9%) |
| Neonatal data   |               |
| Gender          |               |
| Male            | 188 (63%) |
| Female          | 109 (37%) |
| Age of BCP      |               |
| Early-onset (<72 hours) | 82 (28%) |
| Late-onset (4–30 days) | 215 (72%) |
| Birth weight    |               |
| VLBW (≤1500 g)  | 92 (31%)   |
| LBW (1501–2500 g) | 67 (23%)   |
| Normal (>2500 g) | 138 (46%)  |

PROM – premature rupture of membranes; BCP – bacterial cytological profiling; VLBW – very low birth weight; LBW – low birth weight.
and co-NS (15%) (Table 2). The spectrum of the pathogens was different among infants with different birth weight ($\chi^2$/$P$, 58.67/$<0.0001$). K. pneumoniae (32%), E. coli (20%), Enterococcus spp (14%), and Candida spp (13%) were the most commonly seen pathogens in very low birth weight infants, and among low birth weight infants E. coli (36%), K. pneumoniae (29%), and Enterococcus spp (12%) were the top 3 isolated bacteria. In normal body weight neonates, E.coli (25%), co-NS (25%), S. agalactiae (15%), and K. pneumoniae (14%) were the most common isolated pathogens (Table 2).

**Clinical characteristic of neonatal sepsis caused by different pathogens**

We analyzed the laboratory findings of neonatal sepsis caused by different pathogens. We found that about 35% of neonatal sepsis patients experienced leukopenia (TLC <7500/ul), in contrast, only 4% of neonate patients experienced leukocytosis (TLC >25 000/ul), and 25% and 29% of neonate patients encountered anemia and thrombocytopenia, respectively. Leukopenia ($>25 000/ul$), and 25% and 29% of neonate patients encountered anemia and thrombocytopenia, respectively. Leukopenia more than 70% of cases caused by K. pneumoniae, Enterococcus spp, or A. baumannii had positive blood cultures within 2 days after admission, while more than 60% of cases caused by K. pneumoniae, Enterococcus spp, or A. baumannii had positive blood cultures more than 3 days from admission.

**Associated risk factors related to neonatal sepsis caused by a given pathogen**

Risk factors associated with neonatal sepsis caused by a given pathogen were evaluated with univariate and multivariate analysis. Vaginal delivery and low birth weight were the risk factor for E. coli infection, with an adjusted odds ratio (AOR) of 2.43 ($P=0.048$) and 1.75 ($P=0.038$) (Table 4), respectively. These results indicated that neonates born by vaginal delivery were 2.43 times more likely to develop E. coli-related sepsis compared to other delivery methods, and neonates with birth weight $<2500$ g were 1.75 times more likely to develop E. coli-related sepsis compared to normal birth weight neonates. Low birth weight was a risk factor for K. pneumoniae infection, with an AOR of 3.078 ($P=0.024$) (Table 4), indicating that neonates with birth weight $<2500$ g were 3.078 times more likely to develop K. pneumoniae-related...
Tables 2. Bacteria composition of neonatal sepsis with different clinical characteristics.

| Species          | E. coli | K. pneumoniae | Co-NS | Enterococcus | S. agalactiae | S. aureus | Candida | A. baumannii | Total | χ², P |
|------------------|---------|---------------|-------|--------------|--------------|-----------|---------|--------------|-------|-------|
| Gender           |         |               |       |              |              |           |         |              |       |       |
| Male             | 48      | 45            | 29    | 22           | 8            | 17        | 11      | 8            | 188   | 17.87, 0.0126 |
| (26%)            | (24%)   | (15%)         | (12%) | (4%)         | (9%)         | (6%)      | (4%)    |              |       |       |
| Female           | 28      | 23            | 17    | 9            | 19           | 6         | 6       | 1            | 109   |       |
| (26%)            | (21%)   | (16%)         | (8%)  | (18%)        | (5%)         | (5%)      | (1%)    |              |       |       |
| Gestational age  |         |               |       |              |              |           |         |              |       |       |
| Preterm (<37 weeks) | 41    | 52            | 14    | 21           | 8            | 15        | 5       | 165          | 42.96, 0.0001 |
| (25%)            | (31%)   | (8%)          | (13%) | (6%)         | (5%)         | (9%)      | (3%)    |              |       |       |
| Term (≥37 weeks) | 35      | 16            | 32    | 10           | 19           | 14        | 2       | 4            | 132   |       |
| (26%)            | (12%)   | (24%)         | (8%)  | (14%)        | (11%)        | (2%)      | (2%)    |              |       |       |
| Mode of delivery |         |               |       |              |              |           |         |              |       |       |
| Vaginal          | 57      | 32            | 30    | 12           | 18           | 12        | 13      | 3            | 177   | 23.82, 0.0012 |
| (32%)            | (18%)   | (17%)         | (7%)  | (10%)        | (10%)        | (7%)      | (7%)    |              |       |       |
| Caesarian section| 19      | 36            | 16    | 19           | 9            | 11        | 4       | 6            | 120   |       |
| (16%)            | (30%)   | (13%)         | (16%) | (8%)         | (9%)         | (9%)      | (3%)    |              |       |       |
| PROM             | 28      | 18            | 10    | 11           | 8            | 2         | 3       | 1            | 81    |       |
| (35%)            | (22%)   | (12%)         | (14%) | (10%)        | (10%)        | (2%)      | (4%)    |              |       |       |
| Intrauterine distress | 5       | 7             | 5     | 1            | 3            | 2         | 2       | 2            | 27    |       |
| (19%)            | (26%)   | (19%)         | (4%)  | (11%)        | (7%)         | (7%)      | (7%)    |              |       |       |
| Age of BCP       |         |               |       |              |              |           |         |              |       |       |
| Early-onset (<72 hours) | 26 | 6             | 14    | 10           | 22           | 2         | 1       | 1            | 82    | 62.75, <0.0001 |
| (32%)            | (8%)    | (17%)         | (12%) | (27%)        | (2%)         | (1%)      | (1%)    |              |       |       |
| Late-onset (4–30 days) | 50   | 62            | 32    | 21           | 5            | 21        | 16      | 8            | 215   |       |
| (23%)            | (29%)   | (15%)         | (10%) | (2%)         | (10%)        | (7%)      | (4%)    |              |       |       |
| Birth weight     |         |               |       |              |              |           |         |              |       |       |
| VLBW (≤1500 g)   | 18      | 30            | 7     | 13           | 2            | 7         | 12      | 3            | 92    | 58.61, <0.0001 |
| (20%)            | (32%)   | (8%)          | (14%) | (2%)         | (8%)         | (13%)     | (3%)    |              |       |       |
| LBW (1501–2500 g) | 24    | 19            | 4     | 9            | 4            | 3         | 2       | 67           |       |       |
| (36%)            | (29%)   | (6%)          | (12%) | (6%)         | (4%)         | (4%)      | (3%)    |              |       |       |
| Normal (>2500 g) | 34      | 19            | 35    | 10           | 21           | 13        | 2       | 4            | 138   |       |
| (25%)            | (14%)   | (25%)         | (7%)  | (15%)        | (9%)         | (2%)      | (3%)    |              |       |       |

PROM – premature rupture of membranes; BCP – bacterial cytological profiling; VLBW – very low birth weight; LBW – low birth weight.

In this retrospective study, we presented the clinical and microbiological data of neonates with positive blood cultures for bacteria conforming sepsis. We first analyzed the composition of pathogens of neonatal septicemia. Among 1048 isolated pathogens, co-NS was the most commonly isolated bacteria, followed by K. pneumoniae and E. coli. This was in accordance with results from several previous studies [11,13,18,19].

Sepsis compared to normal birth weight neonates. Low birth weight and vaginal delivery were risk factors for Candida spp infection, with AOR of 10.286 (P<0.001) and 2.22 (P=0.044) respectively (Table 4). These results suggest that neonates with birth weight <2500 g were 10.286 times more likely to develop Candida spp-related sepsis compared to normal birth weight neonates; in addition, neonates born by vaginal delivery were 2.22 times more likely to develop Candida spp-related sepsis compared to other delivery methods. Being male, preterm labor, and low birth weight neonates were at low risk of S. agalactiae infection, the AOR was 0.217 (P=0.041), 0.209 (P=0.047), and 0.218 (P=0.043) (Table 4), respectively. These results indicated that preterm male neonates with low birth weight were less likely to develop S. agalactiae-related sepsis.

Discussion

In this retrospective study, we presented the clinical and microbiological data of neonates with positive blood cultures for bacteria conforming sepsis. We first analyzed the composition of pathogens of neonatal septicemia. Among 1048 isolated pathogens, co-NS was the most commonly isolated bacteria, followed by K. pneumoniae and E. coli. This was in accordance with results from several previous studies [11,13,18,19].
Co-NS is a commensal organism of the skin; positive blood cultures growing co-NS may be contamination due to inappropriate clinical procedures. Only a small percentage of blood cultures growing co-NS (ranging from 10% to 30%) are considered to be true positive results [18]. In our study, of the 134 cases infected with co-NS with detailed clinical data, only 46 cases presented with symptoms of sepsis: persistent fever, significant change of WBC count, or increase of PCT or CRP level. The true positive rate of blood cultures growing co-NS was about 30% in our study. This rate may be an underestimation, as the immature immunity of neonates might lead to symptomless infections. Positive blood cultures growing co-NS should be dealt with prudently, as several studies have demonstrated that co-NS is one of the most commonly isolated organisms in neonatal intensive care unit [8,20–22]. Empirical antibiotic treatment is standard practice for neonates suspected of septicemia. Nonetheless, early antibiotic exposure remains controversial due to the possibility of creating an environment for emerging bacterial resistance and the potential for poor prognosis [12,23,24]. Thus, it is of great importance to identify which patients that need antibiotic treatment and what kind of antibiotics are most suitable. Isolation of organisms from blood culture is the gold standard for diagnosis of sepsis, but can be time-consuming and false-negative blood culture results make it difficult to guide the choice of antibiotics.

Co-NS is a commensal organism of the skin; positive blood cultures growing co-NS may be contamination due to inappropriate clinical procedures. Only a small percentage of blood cultures growing co-NS (ranging from 10% to 30%) are considered to be true positive results [18]. In our study, of the 134 cases infected with co-NS with detailed clinical data, only 46 cases presented with symptoms of sepsis: persistent fever, significant change of WBC count, or increase of PCT or CRP level. The true positive rate of blood cultures growing co-NS was about 30% in our study. This rate may be an underestimation, as the immature immunity of neonates might lead to symptomless infections. Positive blood cultures growing co-NS should be dealt with prudently, as several studies have demonstrated that co-NS is one of the most commonly isolated organisms in neonatal intensive care unit [8,20–22]. Empirical antibiotic treatment is standard practice for neonates suspected of septicemia. Nonetheless, early antibiotic exposure remains controversial due to the possibility of creating an environment for emerging bacterial resistance and the potential for poor prognosis [12,23,24]. Thus, it is of great importance to identify which patients that need antibiotic treatment and what kind of antibiotics are most suitable. Isolation of organisms from blood culture is the gold standard for diagnosis of sepsis, but can be time-consuming and false-negative blood culture results make it difficult to guide the choice of antibiotics for empirical treatment.

Table 3. Clinical characteristics of neonatal sepsis caused by different pathogens.

| Species      | E. coli (N=76) | K. pneumoniae (N=68) | Co-NS (N=46) | Enterococcus (N=31) | S. agalactiae (N=27) | S. aureus (N=23) | Candida (N=17) | A. baumannii (N=9) |
|--------------|----------------|----------------------|--------------|---------------------|---------------------|------------------|----------------|-------------------|
| hs-CRP level |                |                      |              |                     |                     |                  |                |                   |
| <6 mg/mL     | 32 (42%)       | 7 (10%)              | 18 (39%)     | 13 (42%)            | 14 (52%)            | 3 (13%)          | 7 (41%)        | 1 (11%)           |
| 6–50 mg/mL   | 25 (33%)       | 26 (38%)             | 26 (56%)     | 12 (39%)            | 12 (37%)            | 11 (49%)         | 11 (47%)       | 2 (22%)           |
| >50 mg/mL    | 19 (25%)       | 30 (44%)             | 2 (4%)       | 6 (19%)             | 3 (11%)             | 8 (35%)          | 2 (12%)        | 3 (33%)           |
| PCT level    |                |                      |              |                     |                     |                  |                |                   |
| <0.1 ng/mL   | 9 (12%)        | 3 (4%)               | 3 (7%)       | 1 (3%)              | 0 (0%)              | 3 (13%)          | 2 (12%)        | 1 (11%)           |
| 0.1–0.5 ng/mL| 18 (24%)       | 7 (10%)              | 14 (30%)     | 15 (48%)            | 6 (22%)             | 10 (43%)         | 8 (47%)        | 0 (0%)            |
| >0.5 ng/mL   | 42 (55%)       | 47 (69%)             | 26 (57%)     | 12 (39%)            | 21 (78%)            | 8 (35%)          | 7 (41%)        | 5 (56%)           |
| Routine blood test |     |                      |              |                     |                     |                  |                |                   |
| Leukopenia   | 32 (42%)       | 28 (41%)             | 14 (30%)     | 10 (32%)            | 9 (30%)             | 3 (13%)          | 8 (47%)        | 2 (22%)           |
| Leukocytosis | 7 (1%)         | 4 (6%)               | 1 (2%)       | 1 (3%)              | 1 (4%)              | 1 (4%)           | 1 (6%)         | 1 (11%)           |
| Anemia       | 11 (14%)       | 27 (40%)             | 9 (20%)      | 11 (35%)            | 7 (7%)              | 2 (26%)          | 6 (41%)        | 0 (0%)            |
| Thrombocytopenia | 42 (25%) | 36 (53%)             | 7 (15%)      | 6 (19%)             | 1 (4%)              | 1 (4%)           | 1 (6%)         | 1 (33%)           |
| Mild         | 11 (14%)       | 6 (9%)               | 2 (3%)       | 2 (4%)              | 0 (0%)              | 2 (12%)          | 3 (18%)        | 0 (0%)            |
| Moderate     | 4 (5%)         | 8 (12%)              | 5 (11%)      | 4 (13%)             | 0 (0%)              | 3 (18%)          | 0 (0%)         | 0 (0%)            |
| Severe       | 2 (3%)         | 10 (15%)             | 1 (2%)       | 0 (0%)              | 0 (0%)              | 3 (13%)          | 4 (23%)        | 0 (0%)            |
| Very severe  | 3 (4%)         | 11 (16%)             | 1 (2%)       | 0 (0%)              | 0 (0%)              | 2 (12%)          | 0 (0%)         | 0 (0%)            |

CRP – C-reactive protein; PCT – procalcitonin; TLC – total leukocytes count; Hb – hemoglobin; PLT – platelet count.

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).
In our study, we found that male neonates were diagnosed with sepsis more frequently than female neonates (188 versus 109). This finding was consistent with the results of studies conducted in the USA [12,25]; we do not know the reason for this phenomenon. Except for the different incidence rates of sepsis, the distribution of S. agalactiae among genders has been found to be imbalanced. Female infants appear to be more vulnerable to S. agalactiae, which is the most common pathogens of early-onset neonatal sepsis [9,12]. Here we found more than 80% of neonatal septicemia caused by S. agalactiae were classified as early-onset sepsis, and more than 70% of these cases were term, normal birth weight neonates and most were delivered vaginally. Penicillin may be considered preferentially for empirical treatment of such populations with suspected sepsis.

K. pneumoniae and E. coli were the most common isolated Enterobacteriaceae in our study, accounting for 48% of all the isolated pathogens. Vaginal delivery and low birth weight are the risk factor for K. pneumoniae and E. coli related sepsis. Previous studies demonstrated that most of isolated K. pneumoniae and E.coli from neonatal sepsis patients were ESBL (extended specturm beta-lactamase) producing strains [2,26,27]. We found that about 62%of the isolated K. pneumoniae and E. coli are ESBL positive, thus we should consider this when choosing antibiotics for empirical treatment for patients with high risk of K. pneumoniae or E. coli sepsis. Fungi are common pathogens of neonatal sepsis, implicating in increasing number of systemic infections, usually acquired during prolonged hospital stay of preterm neonates [28]. It is the third most common cause of late-onset neonatal sepsis in low birth weight infants [29]. In our study, Candida spp accounted for 5% of isolated pathogens, significantly higher than the results of 2 other studies conducted in east and southwest China [11,13]. Very low birth weight and vaginal delivery are risk factor for Candida spp related neonatal sepsis. The isolation rate of S. aureus in our study was lower than that reported previously by others [13,26]. Different hygiene levels and different locations of studies may explain the differences in S. aureus isolation rates.

In our study, we found that infants infected with K. pneumoniae, Enterococcus, S. aureus, and A. baumannii had long hospital stays before a positive blood culture for bacteria, indicating that these pathogens were acquired in the hospital. K. pneumoniae is considered normal gastrointestinal flora and has recently been demonstrated as a significant cause of nosocomial infection. Particularly, preterm neonates are vulnerable to K. pneumoniae. Long hospital stays, prolonged intravenous access, endotracheal intubation, or other invasive procedures place preterm neonates at increased risk for hospital-acquired infections.

Table 4. Univariate and multivariate analysis on risk factors associated with indicated pathogen related neonatal sepsis.

| Pathogen          | Risk factor                      | Univariate analysis | P-value | Multivariate analysis | P-value |
|-------------------|----------------------------------|---------------------|---------|-----------------------|---------|
| **E. coli**       | Gender (Male)                    | 1.039               | 0.863   | 0.967                 | 0.782   |
|                   | Gestational age (<37 weeks)      | 0.608               | 0.534   | 0.896                 | 0.613   |
|                   | Mode of delivery (vaginal)       | 3.157               | 0.007   | 2.436                 | 0.048   |
|                   | Birth weight (≤2500 g)           | 2.305               | 0.0289  | 1.756                 | 0.038   |
| **K. pneumoniae** | Gender (Male)                    | 1.232               | 0.216   | 1.075                 | 0.356   |
|                   | Gestational age (<37 weeks)      | 1.398               | 0.148   | 1.137                 | 0.281   |
|                   | Mode of delivery (vaginal)       | 0.5                 | 0.058   | 0.78                  | 0.08    |
|                   | Birth weight (≤2500 g)           | 3.547               | 0.017   | 3.078                 | 0.024   |
| **Candida**       | Gender (Male)                    | 1.106               | 0.659   | 1.006                 | 0.775   |
|                   | Gestational age (<37 weeks)      | 0.89                | 0.765   | 0.932                 | 0.586   |
|                   | Mode of delivery (vaginal)       | 2.781               | 0.027   | 2.212                 | 0.044   |
|                   | Birth weight (≤2500 g)           | 11.654              | <0.001  | 10.286                | <0.001  |
| **S. agalactiae** | Gender (Male)                    | 0.356               | 0.047   | 0.217                 | 0.041   |
|                   | Gestational age (<37 weeks)      | 0.261               | 0.047   | 0.209                 | 0.047   |
|                   | Mode of delivery (vaginal)       | 1.346               | 0.123   | 1.156                 | 0.354   |
|                   | Birth weight (≤2500 g)           | 0.314               | 0.056   | 0.218                 | 0.043   |
Systemic bacterial infection may lead to malfunctions of the hemopoietic system. In our study, of the 297 cases with detailed clinical and microbiological data, 105 cases experienced leukopenia and only 11 cases experienced leukocytosis. This was not our expectation, as leukocytosis is considered one of the indices of sepsis [30]. Anemia and thrombocytopenia occurred in 73 and 89 cases of sepsis, respectively. These results demonstrated that the hemopoietic system was inhibited under condition of sepsis. In an immature neonatal hemopoietic system, LPS and toxins of the bacteria may be the reasons for hemopoietic malfunction. In our study, *S. aureus* led to less leukopenia than other bacteria. Sepsis caused by *K. pneumoniae* or *Candida* was accompanied by high incidence of anemia and thrombocytopenia. When dealing with neonatal sepsis patients, we should pay attention to hemopoietic changes and take necessary steps to improve the condition of patients.

As our retrospective study, we did not calculate the precise rate of sepsis. Though preterm labor, low birth weight and PROM have been shown to be risk factors for neonatal sepsis, in our study, we found little difference between term and preterm, as well as between low birth weight and normal birth weight; and PROM was only presented in about 25% of the cases. Differences in study design may explain the differences in study results. The obtain more detailed information related with these aspects of neonatal sepsis, a prospective study should be conducted in our hospital.

Though our study has several limitations, it also provides helpful information: it unveils the pathogen composition of neonatal sepsis in our region for the first time, which is of great help in preventing and treating neonatal sepsis. It may be used to guiding the selection of antibiotic for empirical treatment in case characteristic dependent manner.

**Conclusions**

The bacterial spectrum of neonatal sepsis varies among healthcare settings; thus, it is of great importance to find out the bacterial spectrum of neonatal sepsis in a hospital setting for empirical treatment or preventing purposes. The risk factors associating with pathogen-specific sepsis are different based on the pathogen. It is important to consider the possible bacterial spectrum as it might help in choose appropriate treatments. Different pathogens may lead to different clinical manifestations, such as thrombocytopenia, and thus we might conduct appropriate precautionary treatment according to isolated pathogens.

**References:**

1. Wynn JL, Wong HR, Shanley TP et al: Time for a neonatal-specific consensus definition for sepsis. Pediatric Crit Care Med, 2014; 15: 523–28
2. Paolucci M, Landini MP, Sambri V: How can the microbiologist help in diagnosing neonatal sepsis? Int J Pediatr; 2012; 2012: 120139
3. Qazi SA, Stoll BJ: Neonatal sepsis: A major global public health challenge. Pediatr Infect Dis J, 2009; 28: 51–2
4. Stoll BJ, Hansen NI, Sanchez PJ et al: Early onset neonatal sepsis: The burden of group B Streptococcal and E. coli disease continues. Pediatrics, 2011; 127: 817–26
5. Thaver D, Zaidi AK: Burden of neonatal infections in developing countries: A review of evidence from community-based studies. Pediatr Infect Dis J, 2009; 28: 53–9
6. Al-Taira A, Hammoud MS, Liu CQ et al: Neonatal infections in China, Malaysia, Hong Kong and Thailand. Arch Dis Child-Fetal, 2013: 98: F249–55
7. Van Den Hoogen A, Gerards LJ, Verboon-Maciolek MA et al: Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology, 2010; 97: 22–28
8. Bizzarro MI, Shabanova V, Baltimore RS et al: Neonatal sepsis 2004–2013: The rise and fall of coagulase-negative staphylococci. J Pediatr, 2015; 166: 1193–99
9. Verani ML Jr., Schrag SJ: Division of bacterial diseases NCfI, respiratory diseases CDC, prevention. Prevention of Perinatal Group B Streptococcal Disease – revised guidelines from CDC. 2010. MMWR Recomm Rep, 2010; 59: 36
10. Ghotaslou R, Ghorashi Z, Nahaei MR: K. pneumoniae in neonatal sepsis: A 3-year-study in the pediatric hospital of Tabriz, Iran. Jpn J Infect Dis, 2007; 60: 126–28
11. Jiang YM, Kuang LH, Wang HJ et al: The clinical characteristics of neonatal sepsis infection in southwest China. Internal Med, 2016; 55: 597–603
12. Vangay P, Ward T, Gerber JS, Knights D: Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe, 2015; 17: 553–64
13. Zhou B, Liu X, Wu J et al: Clinical and microbiological profile of babies born with risk of neonatal sepsis. Exp Ther Med, 2016; 12: 3621–25
14. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR: Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics, 2006; 117: 67–74
15. Cordero L, Ayers LW: Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants. Infect Cont Hosp Ep, 2003; 24: 662–66
16. Tarig TM, Rasool E: Emerging trends of bloodstream infections: A six-year study at a paediatric tertiary care hospital in Kabul. Jcp-s-j Coll Physic, 2016; 26: 887–91
17. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR: Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr, 2011; 159: 720–25
18. Gautam V, Sethuraman N, Kaur R et al: Changing epidemiology of coagulase-negative staphylococci in normal flora of skin. Indian J Med Microbiol, 2017; 35: 277–78
19. Zaidi AKM, Thaver D, Ali SA, Khan TA: Pathogens associated with sepsis in newborns and young infants in developing countries. Pediatr Infect Dis J, 2009; 28: 510–18
20. Dong Y, Speer CP: The role of Staphylococcus epidermidis in neonatal sepsis: Guarding angel or pathogenic devil? Int J Med Microbiol, 2014; 304: 513–20
21. Jean-Baptiste N, Benjamin DK, Cohen-Wolkowiez M et al: Coagulase-negative staphylococcal infections in the neonatal intensive care unit. Infect Cont Hosp Ep, 2011; 32: 679–86
22. Marchant EA, Boyce GK, Sadarangani M Lavoie PM: Neonatal Sepsis due to coagulase-negative staphylococci. Clin Dev Immunol, 2013; 5: 586076
23. Alexander VN, Northrup V, Bizzarro MI: Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J Pediatr, 2011; 159: 392–97
24. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR: Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr, 2011; 159: 720–25
25. Shane AL, Sanchez PJ, Stoll BJ: Neonatal sepsis. Lancet, 2017; 390: 1770–80
26. Geyesus T, Moges F, Esthetie S et al: Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatrics, 2017; 17: 137
27. Jyothi P, Basavaraj MC, Basavaraj PV: Bacteriological profile of neonatal septicemia and antibiotic susceptibility pattern of the isolates. J Nat Sci Biol Med, 2013; 4: 306–9
28. Pammi M, Holland L, Butler G et al: Candida parapsilosis is a significant neonatal pathogen: A systematic review and meta-analysis. Pediatr Infect Dis J, 2013; 32: E206–16
29. Benjamin DK, Stoll BJ, Gantz MG et al: Neonatal candidiasis: Epidemiology, risk factors, and clinical judgment. Pediatrics, 2010; 126: E865–73
30. Sharma D, Farahbakhsh N, Shastri S, Sharma P: Biomarkers for diagnosis of neonatal sepsis: A literature review. J Matern Fetal Neonatal Med, 2018; 31: 1646–59