Clinical Characteristics and Predictors of Adverse Outcomes at Discharge in Neonates with Bacterial Meningitis at a Tertiary Hospital in Suzhou, China

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Research Article

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Abstract

Background: Neonatal bacterial meningitis is a severe infectious disease with a high rate of death and neurological complications. Early clinical signs and outcomes are different between preterm and full-term neonates, and little is known about their combined predictors. Therefore, this study aimed to explore the clinical characteristics and predictors of in-hospital outcomes in neonates with bacterial meningitis.

Methods: We retrospectively analyzed hospitalized neonates with bacterial meningitis in the Department of Neonatology, Children's Hospital of Soochow University from January 1,2013 to March 31, 2018. The clinical manifestations, laboratory data, treatment measures, neuroimaging and outcomes at discharge were recorded. Predictors of adverse outcomes were identified by using univariate analyses.

Results: There were 145 neonates diagnosed with bacterial meningitis enrolling in this study, with 39 preterm and 106 full-term neonates. The incidence rate of neonatal bacterial meningitis was 0.56%. There were 28 neonates with birth weight < 2,500 g (19.31%), and 33 neonates presented with an onset of less than 7 days (22.76%). The predominant pathogens were *Escherichia coli* and Group B Streptococcus (accounting for 42.00% and 32.00%, respectively). The median peak fever during the acute illness in full-term neonates was higher than that in preterm neonates ($p<0.05$). The median platelet counts in peripheral blood and white blood cells in cerebrospinal fluid in full-term neonates were higher than those in preterm neonates ($p<0.05$). The positive rate of blood cultures in preterm neonates was higher than that in full-term neonates (71.79% vs. 49.06%, $p=0.02$). The incidence rates of adverse outcomes at discharge were 10/39 (25.64%) and 23/106 (21.69%) in preterm and full-term neonates, respectively. Preterm neonates with bacterial meningitis who had reduced glucose levels in cerebrospinal fluid were more likely to have adverse outcomes at discharge, while full-term neonates who had a bulging anterior fontanel, seizure/convulsions and reduced glucose levels in cerebrospinal fluid were more likely to have worse outcomes.

Conclusions: The incidence rate of hospitalized neonates associated with bacterial meningitis remains high. *Escherichia coli* and Group B Streptococcus were the predominant pathogens in neonatal bacterial meningitis in our region. The risk factor for an adverse outcome at discharge in preterm neonates with bacterial meningitis was a lower cerebrospinal fluid glucose concentration, meanwhile, the risk factors in full-term neonates were a bulging anterior fontanel, seizure/convulsions, and a lower cerebrospinal fluid glucose concentration.

Introduction

The incidence rate of neonatal bacterial meningitis (NBM) has declined in recent years, but it is still a severe infectious disease and a leading cause of adverse sequelae. According to previous studies, the incidence rate of central nervous system infections in neonates varies between 0.3 and 0.38 cases per 1000 live births worldwide [1, 2]. The mortality and long-term neurologic morbidity rate of NBM cannot be ignored [3, 4]. The main clinical manifestations and outcomes may be different between full-team and

preterm neonates. However, neurological sequelae in preterm neonates are associated not only with perinatal infection but also with immature brains [5]. It is helpful to provide timely and prompt management and interventions depending on the early recognition of risk factors for poor prognosis [6]. Exploring the determining etiology, dominant bacteria and risk factors for the adverse outcomes at discharge in neonates with NBM is of great importance. Therefore, this study reviewed the past several years of clinical data of neonates with NBM in Suzhou to explore the risk factors for poor prognosis and assist in the early detection and management of high-risk neonates.

Materials And Methods

We retrospectively reviewed the clinical data of 26917 neonates who were hospitalized at the Department of Neonatology, Children's Hospital of Soochow University from January 1, 2013 to March 31, 2018. This study was approved by the Ethics Committee of Children's Hospital of Soochow University.

Inclusion criteria

Neonates with an onset of bacterial meningitis within the first 28 days of life were enrolled in this study. The inclusion criteria for NBM were as follows [7]: (a) detection or isolation of bacteria from cerebrospinal fluid (CSF) by culture or molecular techniques; (b) detection or isolation of a bacterial pathogen from blood or another normally sterile site recognized to cause meningitis and CSF pleocytosis consistent with bacterial meningitis; and (c) no pathogen or gram isolated from either CSF or peripheral blood, with clinical manifestations and CSF pleocytosis. CSF pleocytosis was defined as $>32\acute{}10^6$/L (day of onset <1 week); $>10\acute{}10^6$/L (day of onset > 1 week); and $>29\acute{}10^6$/L in preterm neonates [8].

Exclusion criteria

Neonates with an onset of NBM after the first 28 days of life were excluded from this study. Additional exclusion criteria were neonates with (a) congenital hydrocephalus or ventricular drain; (b) incomplete clinical information, related laboratory results and head imaging that could not provide data integrity; and (c) chromosomal abnormalities, severe congenital malformation, genetic metabolic diseases, and immune deficiency.

Study allocation

The neonates were allocated into 2 groups depending on gestational age: the full-term neonate group (gestational age ≥ 37 weeks) and the preterm neonate group (gestational age < 37 weeks). The neonates in the 2 groups were also allocated into 2 sub-groups depending on outcomes at discharge:
the complication group and the non-complication group.

Treatment ~~outcome~~ evaluation

Neonates were categorized as healed or improved at discharge if they were asymptomatic and CSF examinations turned normal or basically normal, with no complications. The following short-term

outcomes were assessed at discharge: the occurrence of hearing impairment; abnormal radiological findings; abnormal electroencephalogram (EEG); whether neurosurgical intervention was needed (refer to the neurosurgeon of our hospital after evaluation, the patients were considered to have the indications of lateral ventricle puncture drainage, fluid storage sac placement under the scalp or ventricle shunt); and whether infection-related death occurred during hospitalization (died during hospitalization or died within 3 days after discharge with unplanned discharge).

Data collection

Neonate clinical data included sex, gestational age, day of onset, birth weight, delivery mode and perinatal asphyxia. Maternal data included premature rupture of membranes (PROM), small for gestational age (SGA) and amniotic fluid contamination. The following clinical manifestations during the acute illness were collected: fever, poor feeding, seizures/convulsions, lethargy, apnea, altered muscle tone, and a bulging anterior fontanel. The following laboratory tests were collected: white blood cell (WBC) count, C-reactive protein (CRP), platelet counts, procalcitonin (PCT), gram culture in peripheral blood, protein content, glucose and gram culture in cerebrospinal fluid. Treatments during the acute illness were also collected, including duration of antibiotic use and treatment with corticosteroids, intravenous immunoglobulin, and a CSF drain or reservoir. Radiological findings included brain abscess, cerebral infarcts, hydrocephalus, cerebral hemorrhage, intraventricular hemorrhage, subdural effusion, encephalomalacia and other abnormalities detected by cranial ultrasonography, computed tomography or magnetic resonance imaging before discharge. Brainstem auditory evoked potentials (BAEPs) and EEG results were also collected.

Statistical analysis

SPSS (version 22.0) statistical software (Chicago, United States) was used to analyze the collected data. Variables with a normal distribution were expressed as the mean ± deviation (M±SD). The independent Student's t-test was utilized to compare the variables, and the effect size was the *t* value. Non-normatively distributed variables are expressed as the median and interquartile range (IQR). The Mann–Whitney U test was used for comparisons, and the effect size was the Z value. Numerical variables were represented as percentages (%). The chi-square test was adopted, and the effect value was c^2. The variables with statistical significance in univariate analysis were screened by logistic regression analysis. $P<0.05$ was considered statistically significant.

Results

1. Overview

From January 1,2013 to March 31, 2018, a total of 26917 neonates were admitted to the Neonatology Department, Children's Hospital of Soochow University. A total of 152 neonates were diagnosed with NBM with an incidence rate of 0.56%. A total of 145 neonates met the neonatal bacterial

meningitis criteria and inclusion criteria, including 87 males (60%) and 58 females (40%), 39 preterm neonates (26.9%) and 106 full-term neonates (73.1%), 28 cases with birth weight < 2,500 g (19.31%), 33 cases (22.8%) with early onset (£ 7 days) and 112 cases (77.2%) with late onset (> 7 days). Fifty cases had bacteria detected in CSF culture (34.48%). *E. coli* (n = 21, accounting for 42.00%) and GBS (n = 16, accounting for 32.00%) were the leading pathogens. Thirty-three patients (22.8%) had a poor prognosis at discharge, including 10 preterm neonates (10/39, accounting for 25.64%) and 23 full-term neonates (23/106, accounting for 21.69%) (Table 1).

2. Comparison of clinical characteristics between preterm and full-term neonates

The median peak fever in preterm neonates was lower than that in full-term neonates (38.0℃ vs. 39.0℃, $P<0.05$). The median platelet counts in preterm neonates were significantly lower than those in full-term neonates ($122´10^9$/L vs. $289´10^9$/L, $P<0.05$). The rate of gram detection in blood culture was higher in preterm neonates than in full-term neonates (71.8% vs. 49.1%, $P=0.02$). The median WBC count in CSF in preterm neonates was less than that in full-term neonates (47×10^6/L vs. 320×10^6/L, $P<0.05$) (Table 2).

3. Clinical characteristics and risk factors for poor prognosis at discharge in preterm neonates with bacterial meningitis

3.1. There were 39 preterm neonates with bacterial meningitis, including 19 males (48.72%) and 20 females (51.28%). The median day of onset was 14 days. The median peak fever was 38℃. There were 25 cases with poor feeding (64.10%), 6 cases with seizures/convulsions (15.38%), 21 cases with lethargy (53.85%), 15 cases with altered muscle tone (38.46%), and 9 cases with a bulging anterior fontanel (23.08%). There were 28 preterm neonates with gram detected in blood culture (71.79%), 11 patients that received corticosteroids (28.21%), 19 patients that received intravenous immunoglobulin (48.72%), and 1 patient that received CSF drain or reservoir treatment (2.56%) during the acute illness. The duration of antibiotic use was 39.72±20.02 days (Table 2).

3.2. Comparisons of preterm neonates in the complication and non-complication groups

There were 29 patients with no complications (74.36%) and 10 patients with complications at discharge. There were no statistically significant differences in sex, delivery mode, birth weight, day of onset, incidence of asphyxia, SGA, PROM, or amniotic fluid contamination between the 2 groups ($P>0.05$). There were no significant differences in peak fever, the incidence of poor feeding, seizures/convulsions, lethargy, altered muscle tone, or bulging anterior fontanel between the 2 groups ($P>0.05$). The incidence rate of seizures/convulsions was higher in the complication group ($P<0.05$). The median WBC count in peripheral blood was lower in the complication group than in the non-complication group ($2.84´10^9$/L vs. $10.49´10^9$/L, $P=0.01$). There were no significant differences in CRP, PCT, platelet counts, or gram detection in blood between the 2 groups. The CSF glucose level in the complication group was significantly lower than that in the non-complication group (0.99±0.80 mmol/L vs. 1.95±0.64

mmol/L, *P*<0.05). There were no significant differences in white blood cell count or CSF protein content between the 2 groups (*P*>0.05) (Table 3).

3.3 Multivariate logistic regression analysis of risk factors for complications in preterm neonates with bacterial meningitis

The 3 variables with statistically significant differences in univariate analysis results were included in the multivariate logistic regression analysis. Preterm neonates with bacterial meningitis with reduced glucose levels in CSF were more prone to developing complications at discharge. The area under the curve (AUC) of CSF glucose reduction was 0.838 as a predictor. The confidence interval of the area under the curve was 0.681-0.995, the sensitivity was 0.931, and the specificity was 0.625. The cut-off of the glucose level in CSF was 1.3 mmol/L (Table 4).

4. Clinical characteristics and risk factors for poor prognosis at discharge in full-term neonates with bacterial meningitis

4.1 There were 106 full-term neonates with bacterial meningitis, including 59 males (55.66%) and 47 females (44.34%). The median day of onset was 12 days. The median peak fever was 39°C. There were 51 patients with poor feeding (48.11%), 27 patients with seizures/convulsions (25.47%), 40 patients with lethargy (37.74%), 38 patients with altered muscle tone (35.85%), and 39 patients with a bulging anterior fontanel (36.79%). There were 52 full-term neonates with gram detected in blood (49.06%). There were 23 patients with complications at discharge (21.69%). There were 35 patients that received corticosteroids (33.02%), 49 patients that received intravenous immunoglobulin (46.23%), and 4 patients that received CSF drain or reservoir treatment (3.77%) during the acute illness. The duration of antibiotic use was 32.90±21.11 days (Table 5).

4.2 Comparisons of full-term neonates in the complication and non-complication groups

There were 83 patients with no complications (78.30%) and 23 cases with complications (21.69%) at discharge. There were no statistically significant differences in sex, delivery mode, birth weight, day of onset, incidence of premature rupture of membranes, or amniotic fluid contamination between the 2 groups (*P*<0.05). The median peak fever, incidence of seizures/convulsions, and a bulging anterior fontanel were higher in the complication group than in the non-complication group (*P*>0.05). There were no significant differences in the incidence of poor feeding, lethargy, or altered muscle tone between the 2 groups (*P*>0.05). There were no significant differences in WBC counts, CRP, PCT, platelet counts, or gram detection in peripheral blood between the 2 groups (*P*>0.05). The CSF glucose level in the complication group was significantly lower than that in the non-complication group (1.02±1.01 mmol/L vs. 2.02±0.93 mmol/L, *P*<0.05). The median CSF protein level in the complication group was significantly higher than that in the non-complication group (2.20 g/L vs. 1.49 g/L, *P*<0.05) (Table 5).

4.3. Multivariate logistic regression analysis of risk factors for complications in full-term neonates with bacterial meningitis

The 4 variables with statistically significant differences in univariate analysis results were included in the multivariate logistic regression analysis. Full-term neonates with bacterial meningitis with a bulging anterior fontanel, seizures/convulsions, and reduced CSF glucose levels were more prone to developing complications at discharge. The AUC of a bulging anterior fontanel, seizures/convulsions, and reduced CSF glucose level as predictors of complications at discharge was 0.805. The confidence interval of the area under the curve was 0.691-0.920, the sensitivity was 0.696, and the specificity was 0.866 (Table 6).

Discussion

In this study, we found several differences between preterm and full-term neonates with bacterial meningitis in our hospital. Factors that contribute to poor outcomes at discharge varied between the two groups. Prematurity and birthweight may also determine the prognosis and clinical outcomes. There were no significant differences in treatment measures between preterm and full-term neonates.

In a previous study, nearly half of deaths under 5 years old occurred in the neonatal period, and infectious diseases are one of the leading causes of neonatal deaths [9,10]. Bacterial meningitis is a very serious central nervous infections that can cause wide neurological sequelae [11]. The morbidity rate of bacterial meningitis is 0.08 to 6.0 per 100 in neonates worldwide [12,13,14]. In our study, the incidence rate of NBM was 0.56%, and the incidence rate of poor outcomes at discharge was 22.76% (33/145). In another study, a single-center retrospective study that included 103 neonates, 30% of survivors had neurodevelopmental impairments [15], which was consistent with our findings.

The golden diagnosis rule for pathogenic bacteria detection is the CSF smear or culture. Lumbar puncture should be performed before the initiation of antibiotics. However, in clinical practice, antimicrobial treatment for highly suspicious bacterial meningitis must be used right away; thus, the presence of gram in the CSF would be affected. A multicenter retrospective cohort that enrolled almost all full-term neonates from 2005 to 2017 in Shanghai, China, showed that *E. coli* and GBS were the leading pathogens in bacterial meningitis [16]. In our study, *E. coli* and GBS were the top 2 pathogenic bacteria, which is consistent with this prior study. In developed countries, Group B Streptococci (42%) and *E. coli* (16%) are also the main pathogenic microbes [17].

Preterm neonates need to stay in the hospital for a long period. They are more liable to receiving mechanical ventilation, peripherally inserted central catheters and other invasive operations, which are vulnerable to infectious diseases. Additionally, preterm neonates cannot obtain enough transplacental-derived maternal immunoglobulin, so the incidence rate of bacterial meningitis is higher [18,19].

The clinical features of NBM are nonspecific and depend on the CSF examination, unless the neonates are in critical situations. The major clinical manifestations are poor feeding,
fever, seizures/convulsions, and altered muscle tone; however, these manifestations are difficult to distinguish from neonatal sepsis. When neonate manifest clinical signs of central nervous system infections, severe meningitis is suggested. In our study, we found that poor feeding is the most common clinical sign, present in nearly half of preterm and full-term neonates [20]. We also found that the median

peak fever in full-term neonates is higher than that in preterm neonates. Additionally, the platelet and WBC counts were lower, and the rate of gram-positive detected in blood was higher in preterm neonates than in full-term neonates because full-term neonates have a stronger immune response, which could help to enhance resistance to microorganisms [19].

The incidence rate of adverse outcomes in preterm neonates is higher than that in full-term neonates. Although the pathophysiology is hard to explain and complex, one possible reason is that preterm neonates are more liable for brain injury, such as periventricular-intraventricular hemorrhages, which could damage the blood brain-barrier. This may allow bacteria to pass into the subepithelial blood vessels to the central nervous system[21,22].

Early clinical signs and laboratory examination often suggest the outcomes and prognosis in neonates with bacterial meningitis. In our study, we found that clinical signs of seizures/convulsions were significantly different between the complication and non-complication group both in preterm and full-term neonates, which was consistent with a previous study [23,24]. Seizures are usually subclinical and cannot be recognized in a timely manner even by experienced medical workers. The burden of seizures is high in severe meningitis; thus, we need to identify this symptom rapidly through clinical observation or EEG. In this way, we could enforce therapeutic measures to reduce mortality and alleviate neurological sequelae.

Although we hope to diagnose bacterial meningitis early by isolating pathogens from CSF, this method can be easily influenced and become negative after antibiotic administration.
Additionally, bacterial isolation from CSF has shown poor sensitivity in diagnosing bacterial meningitis. In clinical practice, the diagnosis of bacterial meningitis often depends on the laboratory findings in the CSF, including a microorganism, WBC count, protein content and glucose concentrations. Clinicians or neonatologists also use the microscopic and biochemical changes in the CSF to diagnose meningitis. High CSF protein content indicates a severe condition and poor outcomes in NBM, which is widely accepted [25].

Previous studies have shown that the protein concentration in CSF is higher in preterm neonates than in full-term neonates, and there is a higher protein content in the early stage of life [26,27]. In this study, there was no significant difference in CSF protein content between the 2 groups because of the high vascular permeability of the central nervous system in preterm neonates, which leads to a higher protein content; however, full-term neonates have a stronger inflammatory response, and the protein content increases rapidly, which leads to no significant difference in CSF protein content between the 2 groups [28]. Many studies have shown that there were no differences in the mean glucose level in CSF between preterm and full-term neonates, which was consistent with our study [27,29,30]. When neonates have a central nervous system infection, cytokines and nitric oxide metabolites are generated by the cells, and cytokines can also interfere with and disturb brain cellular mitochondrial function, thus causing increased glucose consumption by anaerobic glycolysis,

which causes the CSF glucose level to drop with subsequent brain injury [31], which is consistent with a previous study [32].

Contributions and limitations

Since previous studies have rarely focused on both preterm and full-term neonates with bacterial meningitis, our study is a new try. Also, it is the first study to explore the risk factors for poor outcomes at discharge depending on clinical features, laboratory findings, and treatment in preterm and full-term neonates. Although this is a retrospective study performed in a single hospital, the results also showed some valuable information about NBM to help clinicians and pediatricians in other regions.

However, limitations are inevitable. The limitations of this study majorly lie in its natural characteristics and the limited number of cases from a single hospital and single clinical center, and thus the results can hardly apply to all neonatal bacterial meningitis cases. Additionally, the neonatal behavioral neurological assessment to further evaluate neonatal neurological outcomes is of great importance yet has not been analyzed in this study, so improvement will be done in our future studies. Lastly, we did not look into the perinatal conditions, such as chorioamnionitis and prenatal treatments of mothers.

Conclusion

The incidence rate of neonatal bacterial meningitis was low. *Escherichia coli* and Group B Streptococcus were also the predominant pathogens in our region. There were differences in clinical manifestations and laboratory examination during the acute illness between preterm and full-term neonates with bacterial meningitis. Preterm neonates with bacterial meningitis with glucose reduction in CSF and full-term neonates with a bulging anterior fontanel, seizures/convulsions, and glucose reduction in CSF may be more prone to adverse outcomes at discharge.

Declarations

Availability of data and materials

The raw dataset analyzed in this study will be made available by the corresponding author upon reasonable request.

Authors' contributions

WHW, YG and ZXW collected and analyzed the clinical data, designed the study and wrote the manuscript. XPZ supervised the study design and execution, performed the final data analyses, and contributed to the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All parents or legal guardians of the participants provided written informed consent. This study was approved by the Ethics Committee of the Children's Hospital of Soochow University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol. 2015;42(1):29-45,
2. Okike IO, Johnson AP, Henderson KL, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United Kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clin Infect Dis. 2014,59(10):150-157.
3. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed. 2003,88(3):173-178.
4. Bedford H, Louvois J, Halket S, et al. Meningitis in infancy in England and Wales: follow up at age 5 years. BMJ. 2001,323(7312):533-536.
5. Edwards AD, Tan S. Perinatal infections, prematurity and brain injury. Current Opinion in Pediatrics, 2006, 18(2):119-24.
6. Teixeira DC, Diniz LMO, Guimarães NS, et al. Risk factors associated with the outcomes of pediatric bacterial meningitis: a systematic review. J Pediatr (Rio J). 2020;96(2):159-167.
7. Ouchenir L, Renaud C, Khan S, et al. The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants. Pediatrics. 2017;140(1):e20170476.

8. Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. J Pediatr. (2011) 158:130–134.
9. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the sustainable development goals. Lancet. 2016;388(10063):3027–35
10. Dev A, Casseus M, Baptiste WJ, et al. Neonatal mortality in a public referral hospital in southern Haiti: a retrospective cohort study. BMC Pediatr. 2022;22(1):81.
11. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011;364(21):2016-2025.
12. Softic I, Tahirovic H, Hasanhodzic M. Neonatal bacterial meningitis: results from a cross-sectional hospitalbased study. Acta Med Acad.2015; 44:117–123.
13. Ben Hamouda H, Ben Haj Khalifa A, Hamza MA, et al. Clinical outcome and prognosis of neonatal bacterial meningitis. Arch Pediatr. 2013;20(9):938-944.
14. Zhao Z, Yu JL, Zhang HB, et al. Five-Year Multicenter Study of Clinical Tests of Neonatal Purulent Meningitis. Clin Pediatr (Phila). 2018;57(4):389-397.
15. Haffner DN, Machie M, Hone E, et al. Predictors of Neurodevelopmental Impairment After Neonatal Bacterial Meningitis. J Child Neurol. 2021;36(11):968-973.
16. Xu M, Hu L, Huang H, et al. Etiology and Clinical Features of Full-Term Neonatal Bacterial Meningitis: A Multicenter Retrospective Cohort Study. Front Pediatr.2019;7:31.
17. Holt DE, Halket S, Louvois J, et al. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed. 2001;84(2):85-89.
18. Baud O, Aujard Y. Neonatal bacterial meningitis. Handb Clin Neurol. 2013; 112:1109-1113.
19. Philbin VJ, Levy O. Developmental biology of the innate immune response: implications for neonatal and infant vaccine development. Pediatr Res. 2009; 65: 98-105.
20. Mauro A, Cortese F, Laforgia N, et al. Neonatal bacterial meningitis: a systematic review of European available data. Minerva Pediatr. 2019;71(2):201-208.
21. Moretti R, Pansiot J, Bettati D, et al. Blood-brain barrier dysfunction in disorders of the developing brain. Front Neurosci. 2015; 9:40.
22. Suthar R, Sankhyan N. Bacterial Infections of the Central Nervous System. Indian J Pediatr. 2019;86(1):60-69.
23. KlingerG, ChinCN, BeyeneJ, et al. Predicting the outcome of neonatal bacterial meningitis. Pediatrics. 2000;106(3):477-482.
24. Mao DH, Miao JK, Zou X, et al. Risk factors in predicting prognosis of neonatal bacterial meningitis-a systematic review. Front Neurol. 2018; 9:929.
25. Tan J, Kan J, Qiu G, et al. Clinical prognosis in neonatal bacterial meningitis: the role of cerebrospinal fuid protein. PLoS ONE. 2015;10:e0141620

26. Wong M, Schlaggar BL, Buller RS, et al. Cerebrospinal fluid protein concentration in pediatric patients: defining clinically relevant reference values. Arch Pediatr Adolesc Med. 2000; 154:827–31.
27. Ahmed A, Hickey SM, Ehrett S, et al. Cerebrospinal fluid values in the term neonate. Pediatr Infect Dis J. 1996; 15:298–303.
28. Shah SS, Ebberson J, Kestenbaum LA, et al. Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants. J Hosp Med. 2011;6(1):22-27.
29. Albuquerque Diniz EM, Spina-França Netto A, Livramento JA, et al. Cerebrospinal fluid in premature newborn infants during the neonatal period. I. Biochemical aspects. Bol Med Hosp Infant Mex. 1982; 39:253–257.
30. Vaz FA, Livramento JA, Spina-França A. Cerebrospinal fluid in the healthy preterm newborn infant. Arq Neuropsiquiatr. 1977; 35:183–188.
31. Noureldein M, Mardare R, Pickard J, et al. Cerebrospinal fluid protein and glucose levels in neonates with a systemic inflammatory response without meningitis. Fluids Barriers CNS. 2018;15(1):8.
32. Kao Y, Tsai MH, Lai MY, et al. Emerging serotype III sequence type 17 group B streptococcus invasive infection in infants: the clinical characteristics and impacts on outcomes. BMC Infect Dis. 2019;19(1):538.

Tables

Table 1

Characteristics of 145 Neonates with Bacterial Meningitis.

Characteristic	Cases (n)	Percentage (%)
Male	87	60.00%
Gestational Age		
Preterm	39	26.90%
Full-term	106	73.10%
Birth weight		
≤2499 g	28	19.31%
>2500 g	117	80.69%
Onset day		
≤6 days	33	22.76%
7-28 days	112	77.24%
Microorganisms from the CSF	50	34.48%
Escherichia coli	21	42.00%
Group B Streptococcus	16	32.00%
Other organisms	13	16.00%
Complications at the end of treatment		
Brain abscess	1	0.69%
Cerebral infarcts	1	0.69%
Hydrocephalus	7	4.83%
Cerebral hemorrhage	10	6.89%
Intraventricular hemorrhage	19	13.10%
Subdural effusion	10	4.83%
Encephalomalacia	6	4.14%
Hearing loss	4	2.76%
Seizure	1	0.69%
Death	2	1.38%

CSF, cerebrospinal fluid.

Table 2

Comparison of Preterm and Full-term Neonates with Bacterial Meningitis.

Characteristic	Preterm (n=39)	Full-term (n=106)	Effective value	P
Clinical manifestation during the acute illness				
Onset day, d, median (IQR)	14.00(4.00–23.50)	12.00(5.00–19.25)	0.76	0.44
Peak fever, ℃, median (IQR)	38.00(37.00–38.60)	39.00(38.50–39.37)	5.26	0.00
Poor feeding, n (%)	25(64.10)	51(48.11)	2.92	0.09
Seizure/convulsions, n (%)	6(15.38)	27(25.47)	1.65	0.26
Lethargy, n (%)	21(53.85)	40(37.74)	3.04	0.09
Altered muscle tone, n (%)	15(38.46)	38(35.85)	0.08	0.85
Bulging anterior fontanel, n (%)	9(23.08)	39(36.79)	2.42	0.16
Laboratory examination during the acute illness				
Peripheral blood				
WBC, $\times 10^9$/L, median (IQR)	9.46(4.70–18.74)	12.12(7.47–16.00)	0.966	0.33
Platelet, $\times 10^9$/L, median (IQR)	122(69–255)	289(201–412)	5.08	0.00
CRP, mg/dl, median (IQR)	30.16(8–84.29)	35.53(9.50–103.46)	0.32	0.75
PCT, *ng/ml*, median (IQR)	4.67(0.75–10.54)	1.86(0.23–9.39)	1.17	0.24
Blood gram-positive, n (%)	28(71.79)	52(49.06)	5.96	0.02
CSF findings				
CSF gram-positive, n (%)	11(28.21)	39(36.79)	0.06	0.12
WBC, $\times 10^6$/L, median (IQR)	47(14–230)	320(46–1824)	3.27	0.00
Protein, g/L, median (IQR)	1.62 (0.83–2.63)	1.59(1.27–2.00)	0.23	0.82
Glucose, mmol/L, mean ± SD	1.84±1.01	1.75±0.77	0.60	0.55
Treatment during the acute illness				
Antibiotic duration, d, median (IQR)	39.72±20.02	32.90±21.11	1.68	0.09
Corticosteroids, n (%)	11(28.21)	35(33.02)	0.31	0.58
Intravenous immunoglobulin, n (%)	19(48.72)	49(46.23)	0.07	0.79
CSF drain, or reservoir, n (%)	1(2.56)	4(3.77)	0.13	0.72
CSF, cerebrospinal fluid; SGA, small for gestational age; IQR, interquartile range;				

SD, standard deviation; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin.

Table 3

Clinical, Laboratory Predictors of In-hospital Complications in Preterm Neonates with Bacterial Meningitis.

Characteristic	No-complications (n=29)	Complications (n=10)	Effective value	P
Male sex, n (%)	13(44.82)	6(60.00)	0.69	0.48
Cesarean section, n (%)	18(62.07)	8(80.00)	1.08	0.45
Birth weight, g, mean ± SD	1834.83±641.36	2228.00±771.33	1.59	0.12
Onset day, d, mean ± SD	17.79±4.51	12.70±11.29	1.01	0.32
Asphyxia, n (%)	9(31.03)	2(20.00)	0.45	0.69
SGA, n (%)	7(24.14)	1(10.00)	0.91	0.42
PROM, n (%)	8(27.59)	5(50.00)	1.68	0.25
Amniotic fluid contamination, n (%)	5(17.24)	1(10.00)	0.00	0.51
Clinical manifestation during the acute illness				
Peak fever, ℃, median (IQR)	38.20(37–38.70)	37(37–38.30)	1.22	0.25
Poor feeding, n (%)	16(55.17)	9(90.00)	3.92	0.06
Seizure/Convulsions, n (%)	1(3.45)	5(50.00)	2.51	0.00
Lethargy, n (%)	14(48.28)	7(70.00)	1.41	0.29
Apnea, n (%)	10(34.48)	4(40.00)	0.10	0.75
Altered muscle tone, n (%)	11(37.93)	4(40.00)	0.01	0.91
Bulging anterior fontanel, n (%)	5(17.24)	4(40.00)	2.17	0.20
Laboratory during the acute illness				
Peripheral blood				
WBC, $\times 10^9$/L, median (IQR)	10.49(5.67–21.68)	2.84(1.60–8.07)	0.19	0.01
Platelet, $\times 10^9$/L, mean ± SD	146.60±117.40	176.50±114.05	0.70	0.49
CRP, mg/dl, median (IQR)	30.18(8.13–89.00)	30.28(7.00–72.00)	0.04	0.99
PCT, *ng/ml,* median (IQR)	3.19(0.73–10.63)	6.09(1–10.46)	0.14	0.90
Blood gram-positive, n (%)	22(75.86)	6(60.00)	0.92	0.42
CSF findings				

WBC, $\times 10^6$/L, median (IQR)	50.00(26.00–200.00)	26.00(10.00–670.00)	0.19	0.87
Protein, g/L, median (IQR)	1.50(1.24–1.93)	2.04(1.66–2.99)	1.82	0.07
Glucose, mmol/L, mean ± SD	1.95±0.64	0.99±0.80	3.59	0.00

CSF, cerebrospinal fluid; SGA, small for gestational age; PROM, premature rupture of membrane; IQR, interquartile range; SD, standard deviation; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin.

Table 4

Multivariate Analyses of Risk Factors for In-hospital Complications in Preterm Neonates with Bacterial Meningitis.

Variables	P	OR	95%CI
Seizure/Convulsions	0.074	17.783	0.758-417.162
Reduced CSF glucose	0.024	0.132	0.023-0.765
Reduced peripheral blood WBC	0.297	4.164	0.285-0.895

CSF, cerebrospinal fluid; WBC, white blood cell.

Table 5

Clinical, Laboratory Predictors of In-hospital Complications in Preterm Neonates with Bacterial Meningitis.

Characteristic	No-complications (n=83)	Complications (n=23)	Effective value	P
Male sex, n (%)	45(54.22)	14(60.87)	0.32	0.64
Cesarean section, n (%)	22(26.51)	8(34.78)	0.61	0.60
Birth weight, g, mean ± SD	3351.33±472.20	3452.48±479.73	0.92	0.36
Onset day, d, mean ± SD	12.45±8.63	15.50±9.53	1.47	0.15
Asphyxia, n (%)	4(4.82)	0	–	–
SGA, n (%)	5(6.02%)	0	–	–
PROM, n (%)	12(14.46)	1(4.35)	1.71	0.29
Amniotic fluid contamination, n, (%)	6(7.23)	1(4.35)	0.24	0.70
Clinical manifestation during the acute illness				
Peak fever, °C, median (IQR)	38.(38.5–39.3)	39.20(39.0–39.6)	2.82	0.01
Poor feeding, n (%)	36(43.37)	15(65.22)	3.44	0.10
Seizure/Convulsions, n (%)	14(16.87)	13(56.52)	14.92	0.00
Lethargy, n (%)	30(36.14)	10(43.48)	0.41	0.63
Altered muscle tone, n (%)	26(31.33)	7(30.43)	3.40	0.09
Bulging anterior fontanel, n (%)	23(27.71)	16(69.57)	13.57	0.00
Laboratory during the acute illness				
Peripheral blood				
WBC, $\times 10^9$/L, median (IQR)	12.28(7.52–16.44)	10.60(3.68–16.07)	1.53	0.13
Platelet, $\times 10^9$/L, mean ± SD	309.10±150.81	176.50±114.05	1.12	0.27
CRP, mg/dl, median (IQR)	37.00(11.00–103.46)	32.50(4.26–107.25)	0.40	0.69
PCT, *ng/ml,* median (IQR)	1.84(0.20–9.71)	2.10(0.59–7.36)	0.15	0.88
Blood gram-positive, n (%)	38(45.78)	14(60.87)	1.64	0.24
CSF findings				
WBC, $\times 10^6$/L, median (IQR)	162.00(37.50–1813.00)	860.00(195–2110)	1.93	0.05
Protein, g/L, median (IQR)	1.49(0.78–2.46)	2.20(1.62–3.40)	2.92	0.00

Glucose, mmol/L, mean ± SD	2.02±0.93	1.20±1.01	3.68	0.00

CSF, cerebrospinal fluid; SGA, small for gestational age; PROM, premature rupture of membrane; IQR, interquartile range; SD, standard deviation; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin.

Table 6

Multivariate Analyses of Risk Factors for In-hospital Complications in Full-term Neonates with Bacterial Meningitis.

Variables	P	OR	95%CI
Bulging anterior fontanel	0.018	3.779	1.257-11.359
Seizure/Convulsions	0.028	3.489	1.144-10.639
Elevated CSF Protein	0.065	0.295	1.451-6.035
Reduced CSF glucose	0.019	0.498	0.277-0.893

CSF, cerebrospinal fluid.