



The Risk Factors of Bacterial Meningitis in Late-Onset Neonatal Sepsis

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Abstract

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BACKGROUND: Neonatal bacterial meningitis has a significant contribution on neonatal morbidity and mortality. It is the most common complication of late-onset neonatal sepsis. An understanding of the risk factors for bacterial meningitis in late-onset neonatal sepsis is required to provide comprehensive management.

AIM: To identify the risk factors of bacterial meningitis in late-onset neonatal sepsis.

METHODS: This is an analytical study with a case-control design, conducted in May 2019-February 2021, involving neonates aged 4–28 days who suffered from late-onset neonatal sepsis in Level II and III Neonatal Care Unit, Sanglah General Hospital Denpasar. Statistical analysis was performed using Chi-square and logistic regression.

RESULTS: A total of 54 patients were analyzed in this study. The mean age of subjects with neonatal bacterial meningitis was 13 days and the majority of them were male (51.9%). The risk factor of bacterial meningitis in late-onset neonatal sepsis was gestational age <37 weeks with odds ratio 4.22 (95% confidence interval 1.28–13.86, $p = 0.01$). There was no significant association of birth weight <2500 g, neonatal asphyxia, and invasive procedure on neonatal bacterial meningitis.

CONCLUSION: Gestational age <37 weeks is a risk factor for bacterial meningitis in late-onset neonatal sepsis.

Background

Neonatal bacterial meningitis is an inflammation of the meninges which happens during the first 28 days of life, with evidence of the presence of bacteria in the cerebrospinal fluid (CSF). The incidence of neonatal meningitis ranges from 0.25 to 1/1000 live births and occurs in 25% of neonates with bacteremia. Approximately 10% of affected infants died and 20–50% of survivors develop seizures, hearing and visual impairments, cognitive problems, and motoric abnormalities [1], [2], [3]. The prenatal risk factors of neonatal bacterial meningitis were premature rupture of membrane, maternal vaginitis, asymptomatic bacteriuria, preterm infants, low birthweight infants, and asphyxia [4].

Neonatal bacterial meningitis is the most common complication of neonatal sepsis. In developing countries, meningitis was found in 2.4–12.7 of 7.1–38 cases of neonatal sepsis per 1000 births [5], [6]. The prevalence of neonatal meningitis in clinical sepsis at the Neonatal Intensive Care Unit, Sanglah General Hospital Denpasar was 68.8% [7]. A study by Arora

et al. also reported 55 cases of meningitis (61.11%) in 90 patients with suspected late-onset neonatal sepsis [8].

Diagnosis of neonatal bacterial meningitis is based on clinical manifestations and examination of CSF. The culture of CSF is the gold standard for diagnosing neonatal bacterial meningitis [4], [6]. Negative CSF culture in most cases of meningitis can be caused by previous use of antibiotics or incompatibility of culture media. Polymerase chain reaction (PCR) examination can be used to detect pathogens in the CSF of patients with a history of previous use of antibiotics. The PCR has a sensitivity of 86%, specificity of 97%, a positive predictive value of 80%, and a negative predictive value of 98% compared to culture [9].

The initial manifestations of neonatal bacterial meningitis and neonatal sepsis are nonspecific and difficult to distinguish [4]. It can cause a delay in diagnosis and in turn, affect the prognosis and survival of patients [10]. The mortality rate in neonates with meningitis in suspected late-onset sepsis was 45.5% [8]. Based on this background, we need to identify the risk factors of bacterial meningitis in late-onset neonatal sepsis at Sanglah General Hospital, Denpasar.

Methods

This is an analytical study with a case–control design (without matching), conducted in May 2019–February 2021, involving neonates aged 4–28 days who suffered from late-onset neonatal sepsis at Level II and III Neonatal Care Unit, Sanglah General Hospital Denpasar. A total of 54 patients participated in this study and these patients were obtained using consecutive sampling method. The exclusion criteria include major congenital anomaly, congenital infection, and intracranial hemorrhage. Data were collected from medical records and laboratory examination results. The case group was neonates with late-onset sepsis and bacterial meningitis, while the control group was neonates with late-onset sepsis and no bacterial meningitis. The data were then analyzed statistically using the Chi-square test and logistic regression.

In this study, neonatal bacterial meningitis is defined as neonates with late-onset sepsis who fulfilled the clinical and CSF analysis criteria, including pleocytosis (>20 leukocytes/ mm^3), dominant polymorphonuclear cells, and/or decreased glucose levels (<20 – 30 mg/dl) or CSF glucose $<2/3$ serum glucose, and/or increased CSF protein levels (>150 mg/dl), and a positive universal primer (16S ribosomal Ribonucleic acid) PCR test as the presence of bacteria, with or without positive CSF culture results [6], [9]. Late-onset neonatal sepsis is defined as a systemic illness accompanied by bacteremia occurring in neonates aged >3 days and characterized by clinical manifestations and at least 2 positive laboratory examinations including leukocytes count <5000 or $>35,000/\mu\text{L}$, neutropenia $<1500/\mu\text{L}$ or neutrophilia, platelets $<150,000/\mu\text{L}$, procalcitonin ≥ 0.05 ng/mL, or (immature to total neutrophil) IT ratio >0.2 , with or without positive blood culture results [6].

Gestational age is defined as the period from conception to the time of birth, calculated from the 1st day of the last menstrual period or assessed for neonates using the New Ballard Score or Finstrom Score. Preterm infant is defined if the baby was born <37 weeks of gestation. Birth weight is the weight of the baby measured within 1 h after birth. Low birth weight is defined as the birth weight of <2500 g regardless of gestation [11]. Neonatal asphyxia is a newborn condition based on the results of the appearance, pulse, grimace, activity, and respiration (APGAR) score examination at the 1st min after birth. Asphyxia is defined if the APGAR score is <7 [12]. Invasive procedure is defined as procedure associated with a technique of inserting a device into the body, including insertion of an umbilical catheter and/or a central venous catheter (peripherally inserted central catheter and/or central venous line) and/or endotracheal intubation [13].

This study has obtained ethical clearance from the Research Ethics Committee of Faculty of

Medicine, Universitas Udayana/Sanglah Hospital (314/UN.14.2.2.VII.14/LP/2019) and the Indonesian Ministry of Health, Directorate General of Health Services (LB.02.01/XIV.2.2.1/13814/2019).

Result

A total of 58 patients with late-onset neonatal sepsis were found during this research period, of which three patients with multiple congenital anomalies and 1 patient with congenital rubella infection were excluded as described in Figure 1. A total of 54 patients were analyzed in this study. The mean age of subjects with neonatal bacterial meningitis was 13 days and the majority of them were male (51.9%). The median gestational age was 33 weeks (minimum–maximum 25–40 weeks) with a mean birth weight of 2035 ± 822 g. Positive blood culture results were obtained in 18.5% of subjects with bacterial meningitis. *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus haemolyticus*, *Klebsiella oxytoca*, and *Serratia marcescens* were found in the blood culture results. Positive CSF culture results were obtained in 3.7% of patients with bacterial meningitis and *Pseudomonas aeruginosa* was found in this result. The presence of neonatal bacterial meningitis was confirmed by a positive result of PCR examination of CSF with universal primer. The characteristics of subjects are described in Table 1.

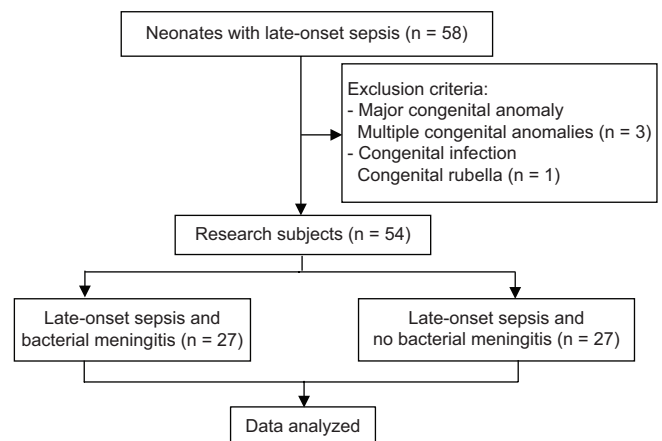


Figure 1: Study flow chart

The risk factor of bacterial meningitis in late-onset neonatal sepsis was gestational age <37 weeks with odds ratio (OR) of 4.22 (95% confidence interval [CI] 1.28–13.86, $p=0.01$). There was no significant association of birth weight <2500 g, neonatal asphyxia, and invasive procedures on neonatal bacterial meningitis in this study. The results of the bivariate and multivariate analysis in this study are shown in Tables 2 and 3.

Table 1: Characteristics of subjects

Characteristics	Bacterial meningitis (n = 27)	No bacterial meningitis (n = 27)
Age, mean ± SD, days	13 ± 6.5	15 ± 7.5
Gender, n (%)		
Male	14 (51.9)	16 (59.3)
Female	13 (48.1)	11 (40.7)
Gestational age, n (%)		
<37 weeks	18 (66.7)	8 (29.6)
≥37 weeks	9 (33.3)	19 (70.4)
Birth weight, n (%)		
<2500 g	17 (63.0)	12 (44.4)
≥2500 g	10 (37.0)	15 (55.6)
Neonatal asphyxia, n (%)		
Asphyxia	11 (40.7)	6 (22.2)
No asphyxia	16 (59.3)	21 (77.8)
Invasive procedure, n (%)		
Invasive procedure	17 (63.0)	16 (59.3)
No invasive procedure	10 (37.0)	11 (40.7)
Blood Panel		
Leukocyte, median (min-max)	15.17 (6.16–53.43)	11.30 (2.15–33.77)
Absolute neutrophil, median (min-max)	8.35 (3.40–42.65)	5.20 (0.65–20.22)
Platelet, mean ± SD	242 ± 188	335 ± 172
IT ratio, median (min-max)	0.18 (0.01–0.87)	0.08 (0.01–2.20)
Procalcitonin, median (min-max)	0.90 (0.10–119)	0.75 (0.07–452)
Blood culture, n (%)		
Growth	5 (18.5)	5 (18.5)
No growth	22 (81.5)	22 (81.5)
CSF cells, n (%)		
≤20 cells/mm ³	4 (14.8)	27 (100)
>20 cells/mm ³	23 (85.2)	0 (0)
CSF glucose, n (%)		
<2/3 blood glucose	27 (100)	0 (0)
≥2/3 blood glucose	0 (0)	27 (100)
CSF protein, n (%)		
≤150 mg/dL	17 (63.0)	22 (81.5)
>150 mg/dL	10 (37.0)	5 (18.5)
CSF culture, n (%)		
Growth	1 (3.7)	0 (0)
No growth	26 (96.3)	27 (100)

CSF=Cerebrospinal fluid, SD=Standard deviation.

Discussion

The proportion of neonatal bacterial meningitis was higher in males (51.9%) with the ratio of males and females of 1.07:1. This finding is similar to the previous study which found a higher incidence of neonatal bacterial meningitis in males [14]. Several studies have shown that there is gender-linked susceptibility to meningitis, in which male is more prone to develop neonatal meningitis. One of the possible explanations is that the factors regulating the synthesis of globulins are situated on the X chromosome. Since male only has one X chromosome, they are less immunologically protected than the females [4], [15], [16].

Table 2: Bivariate analysis of risk factors for bacterial meningitis in late-onset neonatal sepsis

Variable	Bacterial meningitis n = 27	No bacterial meningitis n = 27	OR (95% CI)	p value
Gestational age <37 weeks, n (%)	18 (66.7)	8 (29.6)	4.75 (1.50–15.0)	0.01
Birth weight <2500 g, n (%)	17 (63)	12 (44.4)	2.12 (0.71–6.31)	0.27
Neonatal asphyxia, n (%)	11 (40.7)	6 (22.2)	2.40 (0.73–7.89)	0.24
Invasive procedure, n (%)	17 (63)	16 (59.3)	1.16 (0.39–3.49)	1.0

Lumbar puncture is the main procedure for the diagnosis of neonatal bacterial meningitis. The increase in cells >20 cells/mm³ on CSF examination has a sensitivity of 92.31% and a specificity of 81.48% for the diagnosis of meningitis [17]. However, neonatal

meningitis can occur without an increase in CSF cells due to a wide variation in the normal range of cells based on age and birth weight [18]. In this study, 14.8% of patients with neonatal bacterial meningitis had CSF cells ≤20 cells/mm³. This finding is similar to the previous study which found three cases of neonatal meningitis with CSF cells of <20 cells/mm³ [7].

Table 3: Multivariate analysis of risk factors for bacterial meningitis in late-onset neonatal sepsis

Variable	OR	95% CI	p value
Gestational age <37 weeks	4.22	1.28–13.86	0.01
Neonatal asphyxia	1.60	0.44–5.84	0.47

CSF glucose and protein levels have a lower sensitivity in diagnosing neonatal meningitis. A history of antibiotic administration before CSF examination can affect the results of the CSF glucose and protein levels. Prior administration of antibiotics can lead to high levels of CSF glucose and low levels of CSF protein [19]. In this study, CSF glucose levels were in accordance with the criteria for meningitis, and CSF protein levels of ≤150 mg/dl were found in 63% of subjects with neonatal bacterial meningitis.

In this study, positive blood culture results were obtained in 18.5% of patients with neonatal bacterial meningitis. Positive CSF culture results could be found in 30% of neonates with positive blood culture results [20]. However, in this study, positive CSF culture results were only detected in 3.7% of patients with neonatal bacterial meningitis. In a study of Sharifi-Mood *et al.*, 46 (86.79%) of 53 patients with meningitis had negative CSF culture results. The negative results of CSF culture in most cases of meningitis can be caused by previous use of antibiotics or inappropriate culture media [21].

S. haemolyticus, *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *S. marcescens* were found in the blood cultures of subjects with neonatal bacterial meningitis. These bacteria were not found in the CSF cultures of patients. Group B streptococci (especially type III), *E. coli*, and *Listeria monocytogenes* are the main causes of neonatal meningitis [18]. In this study, *P. aeruginosa* was found in CSF culture results. *P. aeruginosa* is a Gram-negative rod bacteria and a rare cause of neonatal meningitis. The infection of *P. aeruginosa* could be of nosocomial origin [3].

In this study, the presence of bacteria in the CSF of meningitis subjects with no growth culture was identified by PCR examination with universal primer. Positive PCR results were obtained in all subjects whose CSF analysis results fulfilled the diagnosis criteria for neonatal bacterial meningitis. This PCR examination can detect pathogens in CSF higher than CSF culture (72% vs. 48%). In patients with a history of previous use of antibiotics, the ability of PCR to detect pathogens in CSF is also higher than in culture (58% vs. 29%) [22], [23].

The risk factor of bacterial meningitis in late-onset neonatal sepsis was gestational age <37 weeks with OR 4.22 (95% CI 1.28–13.86).

A similar finding was found in a study of risk factors for neonatal meningitis in clinical sepsis [7]. The risks of neonatal bacterial meningitis increase with decreasing gestational age. Preterm infants with sepsis have 3 times higher incidence of central nervous system infections compared to term infants. Immaturity of the neonatal immune system, impaired phagocytic ability of neutrophils and monocytes, and decreased antibodies from the mother contribute to an increased risk of infection in preterm infants. These factors enable the pathogens to be able to reach the meninges through the bloodstream even though the pathogens have a low degree of virulence. The alternative pathway complement system in preterm infants is also ineffective, resulting in impaired defense mechanism against encapsulated bacteria in this population [6], [20], [24]. The development of the blood–brain barrier occurs at the end of gestation and continues into the period after birth. The increased permeability of the developing blood–brain barrier may also increase the susceptibility to infection [25].

Birth weight of <2500 g, neonatal asphyxia, and invasive procedures were not independent factors of bacterial meningitis in late-onset neonatal sepsis. This is possibly because there is no significant difference in the number of neonates without bacterial meningitis, both in the birth weight group <2500 g and ≥2500 g (44.4% vs. 55.6%). Furthermore, the percentage of non-asphyxia neonates with bacterial meningitis was higher (59.3%) compared to neonates with asphyxia and there was no significant difference in the number of neonates who received invasive procedures, both in bacterial meningitis and no bacterial meningitis groups (63% vs. 59.3%). The limitations of this study include the case-control study design without matching and the diagnosis using PCR examination which only determined the presence of bacteria in the CSF. Consequently, further studies with prospective cohort design are needed to identify the other risk factors of bacterial meningitis and also examination of bacterial species through the PCR sequence of CSF patients with neonatal bacterial meningitis.

Conclusion

Gestational age of <37 weeks is a risk factor for bacterial meningitis in late-onset neonatal sepsis. The understanding of this risk factor is important to determine the policy for the comprehensive management of neonates with late-onset sepsis, especially on the prevention of bacterial meningitis.

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