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CHARACTERISTICS OF RISK FACTORS FOR BACTERIAL MENINGITIS IN NEONATES AT RSUP PROF. DR. I.G.N.G NGOERAH DENPASAR

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ABSTRACT

Bacterial meningitis in neonates is inflammation of the meninges in response to bacteria that can occur during the first 28 days of life. Bacterial meningitis is a serious problem causing neonatal deaths with various influencing factors. This research was conducted to obtain data regarding the characteristics of risk factors for bacterial meningitis in neonates at RSUP Prof. Dr. IGNG Ngoerah Denpasar. This study is retrospective, and data was taken from medical records of neonatal patients treated in the 2021-2022 period. Data are presented descriptively with sample determination using a total sampling technique. Total of 45 data that met the inclusion and exclusion criteria, it was found that most cases of neonatal bacterial meningitis occurred at premature gestational age <37 weeks (64.4%), 0-72 hours age group (64.4%), male gender. (51.1%), low birth weight <2500 grams (64.4%), history of asphyxia (51.1%), clinical respiratory distress (82.2%), clinical neonatal sepsis (100%), clinical jaundice neonatorum (68.9%), and use of ventilator/NIV/CPAP (82.2%). In this study, risk factors for premature rupture of membranes were found (20%), intrauterine infection (35.6%), congenital abnormalities (26.7%), and neonates with clinical seizures (6.7%). Based on the research results, it can be concluded that the characteristic risk factors for neonates with bacterial meningitis, namely birth to mothers with preterm or premature gestational age, are more common in neonates aged 0-72 hours, which are associated with clinical EONS, male gender, LBW, history of asphyxia, clinical respiratory distress, clinical neonatal jaundice, and use of ventilator/NIV/CPAP.

Keywords : Neonatal bacterial meningitis., characteristics., risk factors

INTRODUCTION

Bacterial meningitis in neonates is inflammation of the meninges in response to bacteria that can occur during the first 28 days of life, and neonates have a higher risk of bacterial meningitis than other age groups.[1] Meningitis is still a frightening infection because it causes high mortality and morbidity, especially in developing countries with long-term neurological disabilities.[2] Bacterial meningitis in the neonatal period has a significant impact on neurological disability throughout the world, with a morbidity rate of 20% to 60%. National mortality can reach 40% of cases treated in the neonatal period.[3] Several factors can influence a neonate's susceptibility to this disease. Gestational age of less than 37 weeks, male gender, low birth weight (<2500g), premature rupture of membranes, and intrauterine infection are also risk factors for bacterial meningitis in neonates.[4] Congenital abnormalities or congenital diseases, such as congenital heart defects, are risk factors for bacterial meningitis in neonates. Several conditions can also trigger bacterial meningitis, such as a history of asphyxia, neonatal sepsis, and neonatal seizures.[5] Jaundice in neonates can be a risk factor for sepsis, so in clinical bacterial meningitis, neonates can be found to have jaundice.[6] Respiratory aids, such as ventilators, both before and during bacterial meningitis in neonates, can be a risk factor for poor prognosis.[7]

BACTERIAL MENINGITIS IN NEONATES

The bacteria that cause meningitis in neonates can spread from one person to another, from mother to baby, during pregnancy or childbirth.[8] *Escherichia coli*, *Group B streptococci*, and *Listeria monocytogenes* are the most common bacteria that cause meningitis in neonates.[9]

The pathophysiology of bacterial meningitis is vertical through exposure of bacteria through the maternal genital tract to amniotic fluid after the onset of labor or rupture of membranes, then attaches to the endothelium of the cerebral microvasculature and choroid plexus. The bacteria then enter the CSF, replicating in the subarachnoid space along with the release of bacterial products peptidoglycan and cell wall fragments. These bacteria are then recognized by antigen-presenting cells through an increase in pattern recognition receptors such as Toll-like receptors (TLRs) and activating the transcription factor NFkB (Nuclear Factor kappaB) and the production of inflammatory cytokines increasing pro-inflammatory mediators, causing an increase in large numbers of leukocytes and increased permeability blood brain barrier causes bacterial meningitis.[10]

Fever was the predominant symptom in all cases, accompanied by other nonspecific signs and symptoms, such as poor feeding, decreased sucking reflex, and vomiting. Seizures are the main presentation of neurological symptoms and are one of the specific symptoms of bacterial meningitis in neonates.[11] Cerebrospinal fluid (CSF) culture is the gold standard for diagnosing bacterial meningitis. However, deciding when to perform a lumbar puncture (LP) to obtain and analyze CSF is challenging. Factors complicating the diagnosis of LP include

nonspecific signs and symptoms of neonatal meningitis, cardiorespiratory instability that may preclude positioning the infant for LP, and considerable practice variation. If LP is delayed and the infant is exposed to empiric broad-spectrum antibiotics, the clinical results of CSF bacterial culture may be inconsistent. In this situation, doctors interpret CSF parameters, such as cell count, glucose, and protein levels, to diagnose meningitis.[12]

In general, babies are at higher risk of experiencing neurological complications compared to children or adults. In bacterial meningitis, delay in coming to the hospital increases the risk of subdural effusion, hydrocephalus, hearing loss, and seizure disorders.[9]

There are several characteristics of risk factors for bacterial meningitis in neonates. Maternal risk factors include a premature gestational age of less than 37 weeks because immunity is more vulnerable in a more premature body and has a poor prognosis.[7] Premature rupture of membranes and intrauterine infection can also be maternal risk factors associated with the pathophysiology of exposure to bacterial agents in bacterial meningitis.[13,14] Several studies have shown that there is a gender-related susceptibility to meningitis, where males are more susceptible to neonatal meningitis.[15] In addition, low birth weight <2500g and a history of asphyxia with an APGAR score <7 are also associated as risk factors for neonates for bacterial meningitis.[4] Neonates with bacterial meningitis are also often associated with risk factors for experiencing clinical manifestations of respiratory distress,[16] clinical neonatal sepsis, clinical neonatal seizures,[5] and clinical neonatal jaundice.[6] The use of respiratory aids, namely ventilators, is also a risk factor for the clinical impact of developing bacterial meningitis in neonates.[17]

METHOD

This research is a retrospective study with secondary data collection obtained from tracing medical records of cases of bacterial meningitis in neonates at RSUP Prof. Dr. IGNG Ngoerah Denpasar 2021-2022. The data is presented descriptively by explaining the characteristics of risk factors for bacterial meningitis in neonates at RSUP Prof. Dr. IGNG Ngoerah Denpasar 2021-2022. The sample size involved in this research used total sampling adjusted to the inclusion and exclusion criteria to obtain 45 samples. The data collected from the patient's medical record includes the initials of the baby or mother, laboratory results, gestational age, premature rupture of membranes, intrauterine infection, age of the neonate, gender, birth weight, history of asphyxia, congenital abnormalities, clinical respiratory distress, clinical neonatal sepsis, clinical neonatal seizures, clinical neonatal jaundice, and history of ventilator/NIV/CPAP use. The data was then processed using the Statistical Package for Social Science (SPSS). This research has been approved by the Research Ethics Commission of FK Unud/RSUP Prof. Dr. I G.N.G. Ngoerah Denpasar via an ethical letter number 2453/UN14.2.2.V.1/PT.01.01/2023.

RESULT

The study showed 45 neonatal patients with bacterial meningitis treated at RSUP Prof. Dr. I G.N.G. Ngoerah Denpasar from 2021 to 2022.

Table 1 Characteristics of risk factors for bacterial meningitis in neonates at RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar

Related Factors	Total (n=45) n (%)
Maternal Factors	
Gestational Age	
Premature	29 (64.4)
Mature	16 (35.6)
Premature Rupture of Membranes	
<12 jam	1 (2.2)
12-24 jam	3 (6.7)
>24 jam	5 (11.1)
Tidak	36 (80)
Intrauterine Infection	
Yes	16 (35.6)
No	29 (64.4)
Neonatal Factors	
Neonatal Age	
0-72 hours	29 (64.4)
>72 hours	16 (35.6)
Gender	
Man	23 (51.1)
Woman	22 (48.9)
Birth Weight	
Low Birth Weight	29 (64.4)
Normal Birth Weight	15 (33.3)
Excess Birth Weight	1 (2.3)
History of Asphyxia	
Yes	23 (51.1)

No	22 (48,9)
Congenital abnormalities	
Congenital Heart Defects	4 (8.9)
Other Disorders	8 (17.8)
No Congenital Abnormalities	33 (73.3)
Clinical Respiratory Distress	
Yes	37 (82.2)
No	8 (17.8)
Clinical Neonatal Sepsis	
Early Onset Neonatal Sepsis	29 (64.4)
Late Onset Neonatal Sepsis	16 (35.6)
Clinical Neonatal Seizures	
Yes	3 (6.7)
No	42 (93.3)
Clinical Neonatal Jaundice	
Yes	31 (68.9)
No	14 (31.1)
Use of Ventilator/NIV/CPAP	
Yes	37 (82.2)
No	8 (17.8)

Based on data in Table 1 from maternal factors, namely gestational age, history of premature rupture of membranes, and history of intrauterine infection, it was found that 29 (64.4%) neonates were born preterm or premature (<37 weeks), 16 (35.6%) cases of neonates born at term or mature, and no cases found at term or postmature births. In cases with a history of premature rupture of membranes, 9 cases were found with a history of premature rupture of membranes, namely 1 case (2.2%) with rupture of membranes <12 hours, 3 cases (6.7%) with rupture of membranes 12-24 hours, and 5 cases (11.1%) membranes ruptured >24 hours. Meanwhile, 36 cases (80%) had no history of premature rupture of membranes. In cases of a history of intrauterine infection, there were 16 cases (35.6%) of mothers with a history of intrauterine infection, such as vaginal discharge and urinary tract infections. In comparison, in 29 cases (64.4%), there was no history of intrauterine infection.

In Table 1, neonates with an earlier age, namely 0-72 hours, were found in 29 cases (64.4%), while neonates aged >72 hours to 28 days were found to be fewer in 16 cases (35.6%) this age was associated with a diagnosis of neonatal sepsis. Male neonates were found in 23 cases (51.1%), while females were found in 22 cases (48.9%). Based on birth weight, neonates with low birth weight (<2500 grams) were found in 29 cases (64.4%), neonates with normal birth weight (2500-3999 grams) in 15 cases (33.3%), and neonates with excess birth weight (≥4000 grams) in 1 case (2.2%).

In the data, it was found that 23 (51.1%) neonates with a history of asphyxia had an APGAR score <7, and 22 (48.9%) others had no history of asphyxia. From data on congenital abnormalities, 4 (8.9%) neonates were found with congenital heart defects, 8 (17.8%) with other congenital abnormalities such as down syndrome and congenital hydrocephalus, and 33 cases (73.3%) had no congenital abnormalities. It was found that many cases of neonatal bacterial meningitis occurred in clinical respiratory distress in 37 (82.2%) cases, clinical neonatal sepsis in all cases with EONS in 29 cases (64.4%) and LONS in 16 cases (35.6%), clinical neonatal jaundice in 31 (68.9%) cases, and use of ventilator/NIV/CPAP in 37 (82.2%) cases. Meanwhile, neonates with clinical seizures were only found in 3 (6.7%) cases of neonatal bacterial meningitis.

Table 2 Laboratory results of bacterial meningitis in neonates at RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar

Laboratory	**Total n (%) (n = 45)**
Blood Culture	
Growth	24 (53.3)
No Growth	21 (46.7)
CSF Culture	
Growth	6 (13.3)
No Growth	39 (86.7)

CSF Analysis	
Number of Cells (cells/mm³)	
>20	15 (33.3)
≤20	30 (66.7)
CSF Glucose (mg/dL)	
<60%-80% *blood glucose*	42 (93.3)
≥60%-80% *blood glucose*	3 (6.7)
CSF Protein (mg/dL)	
>100	36 (80)
≤100	9 (20)

Based on laboratory data shown in Table 2, as many as 24 (53.5%) of 45 neonates with bacterial meningitis gave positive results for bacterial growth through blood culture, whereas with CSF culture, positive bacterial growth was only in 6 cases (13.3%) of 45 neonates. The blood culture and CSF culture results found bacterial growth in 3 cases: *Klebsiella pneumonia* and *Elizabethkingia meningoseptica*, *Staphylococcus saprophyticus*, and *Streptococcus dysgalactiae*. Blood culture results of no growth and CSF growth were found in 3 cases: 1 case of *Escherichia coli* and 2 cases of *Staphylococcus haemolyticus*. Meanwhile, from the blood culture results, growth and CSF results showed no growth in 21 cases with bacterial findings, namely *Escherichia coli*, *Staphylococcus epidermidis*, 2 cases of *Coagulase-negative staphylococcus*, 2 cases of *Staphylococcus haemolyticus*, *Staphylococcus aureus*, *Staphylococcus warneri*, 2 cases of *Klebsiella pneumonia*, *Klebsiella oxytoca*, 2 cases of *Bacillus spp*., 3 cases of *Serratia marcescens*, 2 cases of *Enterococcus faecalis*, *Acinetobacter humanis*, and 5 cases of *Acinetobacter baumannii*.

In CSF analysis, cell counts were >20 cells/mm^3 in 15 (33.3%) cases, CSF glucose <60%-80% blood glucose in 42 (93.3) cases, and CSF protein >100 mg/dL in 36 (80%) cases. In 30 cases or 66.7%, the cell count was ≤20 cells/mm^3, diagnosed as partial treatment meningitis because it was accompanied by decreased CSF glucose levels and increased CSF protein. They had received antibiotics before the lumbar puncture.

DISCUSSION

Based on laboratory results, it was found that 24 (53.5%) neonates with bacterial meningitis gave positive results for bacterial growth through blood culture. In contrast, only 6 (13.3%) with CSF culture were positive for bacterial growth. These results are the results of the research also conducted at RSUP Prof. Dr. IGNG Ngoerah Denpasar by Rachman et al. (2017) who found 22 babies with neonatal meningitis; only 2 were found to have positive CSF culture, while the other 20 had negative CSF culture and gram staining.[5]

In the findings of CSF analysis, cell counts were >20 cells/mm^3 in 33.3% of cases, CSF glucose <60%-80% blood glucose in 93.3% of cases, and CSF protein >100 mg/dL in 80% of cases. However, a more significant number of cells was found <20 cells/mm^3 in 66.7% of those diagnosed with partial treatment meningitis. The results of this study are supported by previous research by Şah İpek (2019) about neonatal bacterial meningitis, who obtained a CSF cell count of >21 cells/mm^3 in babies with a gestational age of ≥34 weeks, which had a sensitivity and specificity of around 80% to show confirmation of meningitis, however this could result in misdiagnosis in 13% of babies with confirmed meningitis because neonatal meningitis can also occur with normal CSF parameters without bacteremia. Antibiotic treatment before LP is standard because LP is not performed in all cases. CSF leukocyte values remained elevated without significance in patients with meningitis who were exposed to antibiotics for up to 24-36 hours. However, if there is a delay in laboratory analysis, it can decrease the number of leukocytes in CSF analysis.[18]

Based on maternal risk factors, it was found that most cases of neonatal bacterial meningitis occurred at premature gestational age (<37 weeks), with 29 cases (64.4%). The results of this research are supported by Noviyani et al. (2021) in the Neonatal Care Unit at Sanglah Hospital Denpasar. In this study, of 27 neonatal patients with bacterial meningitis, 18 cases (66.7%) were found with premature gestational age <37 weeks.[4] Based on the history of mothers with premature rupture of membranes (PROM), there were 9 cases with PROM, namely 1 case (2.3%) of membranes ruptured <12 hours, 3 cases (6.7%) with membranes ruptured 12-24 hours, and 5 cases (11.1%) membranes ruptured >24 hours. The results of this study are from previous research conducted by Soni et al. (2023) of a total of 64 cases of neonatal bacterial meningitis, only 12 (18.8%) cases were found with a history of premature rupture of membranes.[19] The results of this study found 16 cases (35.6%) of mothers with a history of intrauterine infections, such as vaginal discharge and urinary tract infections. This result is by research by Liu et al. (2020) stated that the majority of neonatal infections are related to intrauterine infections, and the clinical severity of neonatal bacterial meningitis is related to abnormalities such as intrauterine infection, CSF protein concentration and type of pathogenic bacteria, which requires excellent attention from doctors.[13]

It was found that most cases of neonatal bacterial meningitis occurred in the 0-7 hour neonatal age group, namely 29 cases (64.4%). This grouping is based on the time the neonate is diagnosed or suspected of having neonatal sepsis, where infection in the first 72 hours of life is defined as early-onset neonatal sepsis (EONS), and more than 72 hours is defined as late-onset neonatal sepsis (LONS) and is associated with healthcare-associated transmission.[20]

The study showed that most cases of neonatal bacterial meningitis occurred in males, namely 23 cases (51.1%). These results are supported by previous similar research by Noviyani et al. (2021) which found that the proportion of neonatal bacterial meningitis was higher in males, 14 cases (51.9%) while in females, 13 (48.1%), but with a ratio of males and females that was not much different. Different, namely only 1.07:1, and one possible explanation is that the factor that regulates globulin synthesis is located on the X chromosome. Men have only one X chromosome and are less immunologically protected than women.[4] However, contrary to previous research by Ou-Yang et al. (2023) which found that out of 153 cases of bacterial meningitis in neonates, it was higher in women, namely 53.6%.[21]

It was also found that most cases of neonatal bacterial meningitis occurred in neonates with low birth weight <2500 grams or LBW, namely 29 cases (64.4%). These results are by research by Noviyani et al. (2021) of 27 cases of bacterial meningitis neonates found 63% with birth weight <2500 grams.[4]

Based on the history of asphyxia, there were 23 cases (51.1%) with a history of asphyxia or an appearance, pulse, grimace, activity, and respiration (APGAR) score <7. The results of this study are supported by findings from research conducted in the NICU room at Sanglah Hospital Denpasar by Rachman et al. (2017), who obtained results from a total of 22 cases of bacterial meningitis in neonates, and there were 16 cases (72.7%) of neonates with a history of asphyxia.[5]

Based on congenital abnormalities, it showed that only 4 (8.9%) neonates were found with congenital heart defects and 8 (17.8%) with other congenital abnormalities. Based on research by Huo et al. (2019) one of the risk factors for bacterial meningitis was found, namely congenital abnormalities in the form of congenital heart defects and hydrocephalus, which can occur early in the course of bacterial meningitis or after treatment with antibiotics for several days or weeks.[22]

Based on clinical manifestations, most cases of neonatal bacterial meningitis occurred in neonates with clinical respiratory distress, namely 37 cases (82.2%). These results follow Soni et al. (2023) obtained from 64 cases of bacterial meningitis in neonates. Most of them, namely 52 (81.3%) cases with respiratory distress.[19]

This study found that all cases (100%) of neonatal bacterial meningitis occurred in neonates accompanied by clinical neonatal sepsis. There were 29 (64.4%) cases found in neonates aged 0-72 hours or categorized as Early Onset Neonatal Sepsis (EONS) and 16 other cases (35.6%) in neonates aged more than 72 hours to 28 days of life or categorized as Late-Onset Neonatal Sepsis (LONS). These results are supported by previous Soni et al. (2023) research, of 64 cases of neonatal bacterial meningitis, 43 (67.2) cases had clinical early-onset neonatal sepsis (EONS).[19]

Table 3 Distribution of blood culture results on EONS and LONS in neonates with bacterial meningitis at RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar

Blood Culture	Clinical Sepsis		
	EONS	LONS	Total
Growth	16	8	24
No Growth	13	8	21
Total	29	16	45

Table 3 shows that of the 29 cases of EONS, 16 cases were positive for bacterial growth on blood culture results, while of the total of 16 cases of LONS, 8 cases were positive for bacterial growth on blood culture. Based on research by Walker et al. (2019) the diagnosis of sepsis is a guide for carrying out lumbar puncture as the gold standard for neonatal bacterial meningitis, where LP is performed for all neonates with late-onset neonatal sepsis (more than 72 hours of life); early-onset neonatal sepsis (<72 hours of life) with a positive blood culture or with suspected early-onset neonatal sepsis if symptoms do not improve or worsen despite being given antibiotics for 48-72 hours.[23]

Based on clinical neonatal seizures, there were 3 (6.7%) cases of neonates with clinical neonatal seizures. In the results of this study, seizures were found in only a small number of cases; this can be supported by an explanation of the standard procedure for diagnosing bacterial meningitis. In neonates diagnosed with EONS with a positive blood culture, LP must be performed immediately, and for all cases of LONS, both positive and negative blood cultures, LP must be performed.[23] So, when bacterial meningitis is diagnosed, the neonate may not have experienced a seizure because neonates often experience delayed seizures after bacterial meningitis and experience permanent focal neurological deficits.[9] Another reason is that most neonatal seizures have no clinical signs (clinically silent), such as seizure movements that are not tonic-clonic and are only accompanied by normal-looking movements of the tongue, legs, or eyes. This condition often makes it difficult for health workers to recognize signs of neonatal seizures, and EEG remains the gold standard for detecting neonatal seizures.[24] However, the findings of this study contradict previous research by Ou-Yang et al. (2023) which found seizures as a complication of bacterial meningitis in 33 (61.1%) neonates out of a total of 54 cases, especially *group B streptococcal*.[21]

It was found that most cases of neonatal bacterial meningitis occurred in neonates with clinical neonatal jaundice, namely 31 cases (68.9%). Jaundice in neonates can be a risk factor for neonatal sepsis. In Halisanti and Wildan's (2017) research, jaundice was found in four-fifths of cases of neonatal sepsis. The problem that often arises as a complication of neonatal sepsis is meningitis in neonates.[25]

It was found that most cases of neonatal bacterial meningitis occurred in neonates with a moderate history or who had received respiratory support with a ventilator/NIV/CPAP, namely 37 cases (82.2%). These results are similar to those of previous research by Ou-Yang et al. (2023) Out of 153 neonates with bacterial meningitis, 91 (59.5%) cases were obtained using breathing aids,

namely non-invasive ventilators (NIV), CPAP, intubation, and use of high-frequency ventilator.[21] The results of this study are also based on research by Boskabadi et al. (2020) of 85 bacterial meningitis neonates, 80 (94.12%) experienced respiratory symptoms, 58 neonates (72.5%) required breathing aids, 33 cases had mechanical ventilation, and 25 cases had CPAP.[26]

CONCLUSIONS AND SUGGESTIONS

Based on the results of research on the characteristics of risk factors for bacterial meningitis in neonates at RSUP Prof. Dr. IGNG Ngoerah Denpasar for the 2021-2022 period, found the characteristics of risk factors for neonates with bacterial meningitis, namely birth to mothers with preterm or premature gestational age, more often occurring in neonates aged 0-72 hours which was associated with clinical EONS, male gender, LBW, history of asphyxia, clinical respiratory distress, clinical neonatal jaundice, and use of ventilator/NIV/CPAP. Regarding the results of the research that has been carried out, it is recommended that other researchers study more deeply the factors that play a role in the development of bacterial meningitis in neonates in order to enrich their knowledge of this matter. Further research is also needed with larger samples and using better research designs such as prospective cohort studies to ensure that the characteristics of bacterial meningitis in neonates found in the results of this study are indeed risk factors so that more complete data can be obtained and bias in this study can be achieved controlled.

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