

The characteristics of neonatal sepsis in Low Birth Weight (LBW) infants at Sanglah General Hospital, Bali, Indonesia in 2018



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ABSTRACT

Background: Sepsis is one of the most common causes of mortality and long terms morbidity among infants. It is known to be related to Low Birth Weight (LBW) due to the lack of immunity function to resist the infection. This study aims to identify the characteristics of neonatal sepsis in LBW infants in Sanglah General Hospital.

Method: A retrospective cross-sectional study was conducted in the Neonatal Care Unit, Sanglah General Hospital, during January-December 2018 period among 135 neonates. Samples were taken using total sampling for neonates who had LBW and diagnosed with sepsis. Uncompleted data and voluntarily discharge patients were excluded from the study. Data regarding baseline characteristics of respondents, major and minor risk factors, laboratory results of sepsis, as well as blood culture, were analyzed using SPSS version 23 for Windows.

Result: Most of respondents were male (54.1%), followed by bodyweight 1,500-2,499 grams (58.5%), and preterm labor (<32 weeks) (86.7%). The average length of stay was 21.30±19.28 days. The vast majority of infants diagnosed as Early Onset Sepsis (EONS) (89.6%). Most of the patients had normal leukocyte count (93.3%), neutrophilia (95.6%), low I/T ratio (70.4%), normal platelets (67.4%), and high procalcitonin (98.5%). The blood culture showed the most microorganism was *Enterococcus faecalis* (6.00%) in gram-positive bacteria.

Conclusion: This study found that most of the respondents were male, followed by preterm labor, EONS, normal leukocyte count, low I/T ratio, high procalcitonin, as well as *Enterococcus faecalis* as the most common gram-positive bacteria.

Keywords: Characteristics, Neonatal Sepsis, Low Birth Weight

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INTRODUCTION

LBW is considered as one of the risk factors of infection that occurred among infants.¹ LBW is defined by babies weighing less than 2,500 grams at birth according to gestational age.¹ World Health Organization (WHO) classifies LBW into 3 categories; low birth weight babies (LBW) with the weight less than 2500 grams, Very Low Birth Weight (VLBW) is less than 1500 grams, and very low birth weight (VVLBW), who has a weight less than 1000 grams.² It is known that the prevalence of LBW in the USA is 1.46%, with more than 50% of cases related to death and disability.³ According to Indonesian's Ministry of Health, there were 10.20% of babies (0-59 months) who had LBW with the highest percentage was 16.8% in Central Celebes. Meanwhile, the lowest was 7.2% in North Sumatra.⁴ In Bali, it is estimated that the percentage of LBW in 2013 was 9%.⁴

Preterm Infants are well acquaintance to have a higher risk of developing sepsis, and other sequelae compare to term infants. It is suggested that two-thirds of LBW in developing countries are premature infants.² Neonatal sepsis is one of the most dangerous systemic infection manifestations, which

is defined as a clinical syndrome of systemic infection with bacteremia in the first month of life.^{3,5} In the United States, the data shows that the incidence of early-onset sepsis in VLBW infants was 1.5%, whereas 25% of late-onset sepsis.⁶ The incidence of neonatal sepsis ranges from 1 to 10 cases per 1000 live births and 1 per live birth monthly.⁶ Following Fundamental Health Research data from the Indonesian Ministry of Health (RISKESDAS) in 2007, it was showed that sepsis is a risk factor for neonatal deaths at the age of 0-6 days by 12% and approximately around 20.5% of neonatal mortality at the age of 7-28 days.⁷ Another data in 2010 showed that the incidence rates of neonatal sepsis in referral hospitals in Indonesia are estimated around 1.5%-3.72% with the considerable high mortality rates which are around 37.09%-80%.^{4,7}

Several conditions have been identified as risk factors for sepsis.⁸ These conditions include maternal risk factors, such as premature rupture of membranes (especially more than 18 hours), infection and fever during pregnancy, foul-smelling and or meconium-stained liquor, and multiple pregnancies.⁸ Furthermore, there are also risk factors

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for infants, such as prematurity, LBWR, asphyxia, resuscitation during labor, invasive procedures, congenital abnormalities, parenteral nutrition, and also the length of stay in neonates intensive care unit.⁸ Other risk factors include male gender, black race, and low socioeconomic status.^{8,9} Sepsis is triggered by the microorganism that initiated inflammation cascade, beginning with the release of several inflammation mediators.¹⁰ Naturally, the body will resist the reaction through both the cellular and humoral immune system, including monocytes, macrophages, and neutrophils, antibodies formation and complement pathway activation.^{10,11} Newborns are well acquaintance to have a weaker ability in responding to the infections due to immature immune systems. Low birth weight babies are 2.7 times more likely to develop sepsis due to humoral and cellular immune systems deficiency, and the invasive procedures performed.^{10,11}

Clinical manifestations of infection in newborns are varied, with mild to severe manifestations of focal or systemic infections and congenital syndromes, rarely it can also occur from intra-uterine infections.¹² Exposure time, inoculum size, immune status, and virulence of the causative agent influence the manifestations of the disease. The least the specific symptoms associated with sepsis and the limitations of laboratory criteria are causing the diagnosis of sepsis among the newborns is challenging to establish.¹² Preterm infants and LBW have experienced a significant improvement in their condition, along with the advancement of medical management for them. Nonetheless, long term treatment in the hospital possibly causes the continued risk of getting an infection.

Based on those mentioned above, this study aims to determine the characteristics of neonatal sepsis in LBW in the neonatology room at Sanglah General Hospital, Bali, Indonesia, in 2018.

METHOD

This study was using a descriptive retrospective design with a cross-sectional approach among subjects who were treated in Sanglah General Hospital's neonatal care unit level 2 and 3. This research was held in August 2019, using data that were collected from LBW infants' medical records who also diagnosed with sepsis registered from January 2018 until December 2018. Uncompleted medical records and patients who voluntarily discharged from the hospital were excluded from the study. The sampling technique that was used in this study is a total sampling method.

The variable in this study includes sex, location of delivery, mode of delivery, birth weight, gestational age, parity, length of stay, neonatal sepsis,

outcome, an infection risk factor for neonatal sepsis, infection biomarker. Sepsis is classified as early-onset (<72 hours) and late-onset (>72 hours). The risk factor of sepsis includes mayor and minor risk factors, where the mayor consisted of premature rupture of the membrane more than 24 hours, fever during pregnancy (>38°C), chorioamnionitis, fetal heartbeat more than 160 times per minute, foul-smelling and or meconium-stained liquor. The minor factor consisted of premature rupture of membranes >12 hours, maternal fever at intrapartum (temperature $\geq 37.5^\circ\text{C}$), low APGAR score (minutes 1 <5, minutes 5 <7), VLBW, <37 weeks gestation, multiple pregnancies, vaginal discharge, a mother with urinary tract infection (UTI). Infection biomarkers include procalcitonin, leukocyte, neutrophil, I/T ratio, and blood smear. Infection markers leading to sepsis are leukocytosis ($>34.000 \times 10^3/\mu\text{L}$), leukopenia ($<5 \times 10^3/\mu\text{L}$), neutropenia $<1.5 \text{ K}/\mu\text{L}$, thrombocytopenia ($<150.000/\mu\text{L}$), procalcitonin $\geq 0,05 \text{ ng/mL}$, IT ratio >0.2 and also vacuolization and toxic granule that can be seen from blood smear examination.¹²

Data then analyzed by SPSS 23.0 software. The result will be presented in a descriptive form by a table and narrative explanation. Numerical data with normal distribution were introduced in the median form (minimum-maximum), and data with abnormal distribution are presented in mean form (standard deviation).

RESULT

A total of 135 infants who were registered from January-December 2018 and also fulfilled the inclusion and exclusion criteria were enrolled in this study. General characteristics of the data can be seen in [Table 1](#). Subjects were dominated by males (54.10%), born at Sanglah Hospital (62.20%) by spontaneous birth (51.90%). Most of them weigh 1,500-2,499 grams; in addition, there were 13.30% of them who have birthweight less than 1,000 grams. There were around 86.70% of infants born preterm. Approximately 9.60% of them were born before 28 weeks of gestation ([Table 1](#)).

The mean length of stay was 21.30 ± 19.28 days. The vast majority of infants diagnosed as early-onset sepsis (EONS) (89.6%), whereas the other 10.3% diagnosed as late-onset sepsis (LONS). The mortality percentage of this study was 35.6% ([Table 1](#)).

The risk factors of infection can be seen in [Table 2](#). From the mayor factors, premature rupture of the membrane (PRM) more than 24 hours was the most common factor found among the subjects (11.9%) followed by fetal distress (9.6%) and foul-smelling and or meconium-stained liquor (8.9%).

Table 1 Baseline characteristics of respondents

Variables	Respondents (N=135)
Sex, n (%)	
Male	73 (54.1)
Female	62 (45.9)
Location of Delivery, n (%)	
Sanglah General Hospital	84 (62.2)
Referral	51 (37.8)
Mode of delivery, n (%)	
Spontaneous	70 (51.9)
Forceps extraction	3 (2.2)
Vacuum extraction	0 (0)
Caesarian section	62 (45.9)
Birthweight (Gram), n (%)	
<1,000	18 (13.3)
1,000-1,499	38 (28.1)
1,500-2,499	79 (58.5)
Gestational age (Weeks), n (%)	
<28	13 (9.6)
28-31	41 (30.4)
32-36	63 (46.7)
37	18 (13.3)
Number of Parity, n (%)	
1	75 (55.6)
2	36 (26.7)
>3	24 (17.7)
Length of stay (Days) (Mean±SD)	21.30 (19.28)
Sepsis	
EONS	121 (89.60)
LONS	14 (10.40)
Outcome, n (%)	
Survive	87 (64.4)
Death	48 (35.6)

From minor risk factors, the most common was preterm, with the percentage of 68.1% followed by asphyxia (41.5%) and very low birth weight (37.8%) (Table 2).

Infection markers that were used in this study were leukocyte, neutrophil, I/T ratio, platelets, procalcitonin, and peripheral blood smear. Most of the patients (93.3%) had leukocyte count around 5-34 K/ μ L, neutrophils > 1.5 K/ μ L (95.6%), I/T ratio < 0.2 (70.4%), platelets > 150 K/ μ L (67.4%), and procalcitonin > 0.05ng/ml (98.5%). From the peripheral blood smears, it can be seen that there were 11.1% of subjects with vacuolization and 6.7% with toxic granule. Complete data can be seen in Table 3.

The etiology of infection was seen by using blood culture. Table 4 is showing the result of blood culture that was performed on the subjects. The most common bacteria that can be seen was *Enterococcus faecalis* (6%), followed by *Staphylococcus cohnii* (4.7%) and *Staphylococcus haemolyticus* (3.5%) as gram-positive bacteria. Most of the subjects (71.8%) had a sterile blood culture (Table 4).

DISCUSSION

From the general characteristics of the subjects, it is found that the majority of the subjects were male, born in Sanglah Hospital by spontaneous delivery, weighing 1500-2499 grams, preterm, and null parity. These results are almost familiar with the study conducted by Utomo in 2010, where 61% of the LBW infants with sepsis were male, 44% born by spontaneous delivery, 72% weighing 1500-2499 grams, and 78% preterm.¹ The predominance of male infants in this study possibly caused by a sex-linked factor in the X chromosome.¹³ The gene that is involved in the synthesis immunoglobulin inside the X chromosome has been postulated as a reason behind male predominance, even though most of the study did not show any significantly different in the percentage of male and female infants.¹³

Most of them were diagnosed as early-onset sepsis (EONS). This result is different from a study conducted by Lim WH et al. in China that showed 93.7% of subjects were accounted for as late-onset sepsis.¹⁴ Another study from North Carolina showed that the vast majority of subjects, which were 12.204 infants from 108.000 participants were diagnosed with LONS.⁶ In contrast, another 1032 infants were diagnosed with EONS.⁶ Another study suggested that risk factors for EONS include lower gestational age, female sex, lower APGAR, exposure of antenatal antibiotics, the need for mechanical ventilation on the first day of life and outborn status, whereas for LONS are lower gestational age and exposure to antibiotics.¹⁵ In this study, beside of prematurity, asphyxia which contributes to the APGAR score also have a higher percentage that could be correlated with a higher percentage of EONS in this study.

The mortality percentage of this study was 35.6%. This number is relatively lower than the mortality percentage in Dr. Soetomo General Hospital, where 69.0% of LBW infants with sepsis died during the study.¹ A study conducted in China showed that the case fatality rate of sepsis among VLBW was 7%, which is much lower than this study result.¹⁴ Notwithstanding, they mentioned that infants with early-onset sepsis had a much higher fatality rate than late-onset (40% vs. 5%; $p < 0.01$).¹⁴ This could be a possible explanation about high mortality

Table 2 Infection Risk Factors for Neonatal Sepsis

Variables	Respondents (N=135)
Major risk factors, n (%)	
PRM >24 hours	16 (11.90)
Maternal fever >38°C	3 (2.20)
Chorioamnionitis	0 (0.00)
Fetal distress	13 (9.60)
Foul-smelling and or meconium-stained liquor	12 (8.90)
Minor risk factors, n (%)	
PRM >12 hours	13 (9.60)
Maternal fever >37,5°C	6 (4.40)
Asphyxia	56 (41.50)
VLBW	51 (37.80)
Gestational age <37 weeks	92 (68.10)
Multiple gestations	9 (6.70)
Maternal vaginal discharge	24 (17.80)
Maternal urinary tract infection	7 (5.20)

Table 3 Laboratory Evaluation of Sepsis in Low Birth Weight (LBW) Infants

Laboratorium Parameter	n (%)
Leukocyte, n (%)	
<5 K/ μ L	4 (3.00)
5-34 K/ μ L	126 (93.30)
>34 K/ μ L	5 (3.70)
Leukocyte counts (K/μL) (Mean\pmSD)	13.88 \pm 7.86
Neutrophils, n (%)	
<1.5 K/ μ L	6 (4.40)
\geq 1.5 K/ μ L	129 (95.60)
Neutrophil (K/μL) (Mean\pmSD)	6.87 \pm 6.66
IT Ratio, n (%)	
<0.2	95 (70.40)
>0.2	40 (29.60)
IT ratio (median (min-max))	0.18 (0.01-0.73)
Platelets, n (%)	
<150 K/ μ L	44 (32.60)
\geq 150 K/ μ L	91 (67.40)
Platelets (K/μL) (median (min-max))	186.2 (6.84-521.70)
Procalcitonin, n (%)	
<0.05 ng/mL	2 (1.50)
\geq 0.05 ng/mL	133 (98.50)
Procalcitonin (ng/dL) (Mean\pmSD)	5.11 \pm 21.80
Peripheral blood smear, n (%)	
Vacuolization	15 (11.10)
Toxic granule	9 (6.70)

in this study regarding the domination of EONS cases in this study. Another study also supported that statement where they found that LBW infants who diagnosed with EONS were 1.45 times more likely to be death whereas the risk for LONS was 1.30 times higher in infants.⁶

From the mayor factors, the most common risk factors found were premature rupture of the membrane (PRM) more than 24 hours, fetal distress and foul-smelling, and or meconium-stained liquor. Meanwhile, preterm, asphyxia, and very low birth weight were the top three from minor factors. This result was similar to the literature before. The two most important risk factors for sepsis are preterm, especially birth before 31 weeks (OR=3.9; 95%CI=1.4-11.0) and birth weight less than 1500 grams (OR=5.7; 95%CI=2.5-15.6).¹⁵ Another study suggested that the risk of infection among preterm infants is 11 times higher because of barriers immaturity and incomplete developed immune system.¹⁶ It is believed that preterm infants have immunoglobulin and complement system deficiencies, as well as a lack of opsonization and phagocytosis response by the immune system.¹⁶ The primary factor, premature rupture of the membranes, is known to comorbid 3.0-4.5% of pregnancy but associated with 40% preterm deliveries. This can give an indirect association with sepsis incidence among low birth weight infants.¹⁷

Infection markers leading to sepsis are leukocytosis ($>34.000 \times 10^3/\mu$ L), leukopenia ($<5 \times 10^3/\mu$ L), neutropenia <1.5 K/ μ L, thrombocytopenia ($<150.000/\mu$ L), procalcitonin ≥ 0.05 ng/mL, IT ratio >0.2 and also vacuolization and toxic granule that can be seen from blood smear examination. All those markers are representative of inflammation reactions that occur during infection and sepsis.¹⁸ However, in this study, it is found that most of the patients had a normal leukocyte count, neutrophilia, low I/T ratio, normal thrombocyte count, and high procalcitonin. Some literature stated that the normal count of leukocyte is often seen during the normal infection phase among infants, and it will eventually become normal after 12 hours of onset. The sensitivity of leukocytosis is 17%-90%, with 31%-100% specificity.¹⁵ Normal count in this study perhaps caused by the timing of sample collection. Another study also found that there is an association for normal and low leukocyte count with EONS.¹⁹ This makes perfect sense since the majority of subjects in this study were diagnosed with EONS. Immature to Total neutrophils (I/T) ratio more than 0.2 has a low positive predictive value (PPV) (23.0%) but a high negative predictive value (NVP) (92.0%). This fact may be explained the lower value of the I/T ratio in

Table 4 The Result of Blood Culture

Microorganism	n (%)
Gram-positive bacteria	
<i>Enterococcus faecalis</i>	10 (6.00)
<i>Staphylococcus cohnii</i>	8 (4.70)
<i>Staphylococcus haemolyticus</i>	6 (3.50)
<i>Staphylococcus kloosin</i>	4 (2.40)
<i>Staphylococcus epidermidis</i>	2 (1.20)
<i>Staphylococcus coagulase-negative</i>	1 (0.60)
Gram-negative bacteria	
<i>Pseudomonas aeruginosa</i>	2 (1.20)
<i>Klebsiella pneumonia</i>	2 (1.20)
<i>Acinetobacter baumannii</i>	1 (0.60)
<i>Stenotrophomonas maltophilia</i>	1 (0.60)
<i>Stephanoascus ciferrii</i>	1 (0.60)
Sterile	97 (71.80)

this study. Nonetheless, if the I/T ratio is combined with thrombocytopenia, the PPV will increase to 43% and NVP 96%.¹⁵ A study conducted by Hornik *et al.* found that high I/T ratio and low neutrophils count are associated with increased risk of sepsis among neonates (OR=5.3 and 7.39, respectively).¹⁹ Normal thrombocyte count in this study can be caused by the dominance of EONS among subjects. Hornik *et al.* stated that platelet count does not look helpful as sepsis biomarkers in the setting of EONS due to a small increase in odds of sepsis with thrombocytopenia.¹⁹ In this study, the result of procalcitonin was similar to the other previous studies, wherein neonatal sepsis, the level of procalcitonin, tends to be increased. A study from de Rueda Salguero *et al.* found that the sensitivity of procalcitonin in predicting sepsis is 100% with 95.2% specificity.²⁰

There were only a few subjects who were found to have vacuolization and toxic granules in their peripheral blood smears. Vacuolization and toxic granules are the manifestations of degenerative changes in neutrophils.²¹ As sepsis occurs in the body, neutrophils will increase in number and also change in morphology in order to fight the infection.²¹ A study shows that 60% of infants who had toxic granules and 11% vacuolization were very likely to develop sepsis.¹⁵ It is believed that continued stimulation of neutrophil production and maturation of neutrophils in bone marrow also plays a significant role in the making of degenerative changes among neutrophil cells. However, most of the infants have not had a fully developed *granulopoietic* system yet.²² That fact

could be an answer to the low percentage of sepsis neonates who had vacuolization and toxic granules in this study.

The most common pathogen was gram-positive bacteria. It is similar to the result of Utomo's study that found 100% of the blood culture with bacterial growth showed gram-positive bacteria.¹ A study conducted by Lim *et al.* also showed similar results where gram-positive bacteria caused 60.7% of neonatal sepsis, mostly coagulase-negative staphylococcus/CoNS (52.5%).¹⁴ However, many studies show that CoNS infection more likely to be related to LONS instead of EONS.^{14,15} The most common cause of EONS were gram-negative bacteria (58.2%), followed by gram-positive (34.4%) and *Candida Sp* (2.7%) whereas, 61.4% LONS cases were caused by gram-positive bacteria especially CoNS followed by gram-negative (26.2%) and *Candida* (10.5%).¹⁵ In this study, even though the culture results show gram-positive predominance, the vast majority of subjects diagnosed as EONS. The explanation about that has not been understood yet.

This study has several limitations. This study uses a retrospective descriptive method so that it cannot assess the significance of the results of the study. The study also did not identify patterns of antibiotic sensitivity and resistance, which could also play a role in the outcome of neonatal sepsis. The infection markers listed in this study are when the subject is admitted to the hospital. At the same time, the time is not necessarily the beginning of the appearance of symptoms considering that most of the subjects are referral cases that have been treated in other hospitals that may be in therapy so that the marker of infection cannot real sepsis condition.

CONCLUSION

The recent findings conclude that the characteristics of neonatal sepsis in Low Birth Weight (LBW) infants at Sanglah General Hospital, Bali were dominated by male, spontaneous delivery, 1,500-2,499 grams of bodyweight, 32-36 weeks of gestational age, and Early Onset Sepsis (EONS). Besides, based on the risk of infection, PRM >24 hours was predominant in major risk factors and gestational age <37 weeks for minor risk factors for sepsis. The leukocyte count of 5-34 K/ μ L was dominant in this study. Besides, based on the type of microorganism, *Enterococcus faecalis* was the most frequent in gram-positive bacteria and *Pseudomonas aeruginosa*, as well as *Klebsiella pneumonia* in gram-negative bacteria.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

ETHICS CONSIDERATION

Ethical clearance of this study was given by Bidang Penelitian dan Pengembangan (Litbang) Komisi Etika Penelitian Fakultas Kedokteran Universitas Udayana RSUP Sanglah Denpasar No: 2485/UN.14.2.2.VII.14/LP/2019.

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AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study from the conceptual framework, data gathering, data analysis until reporting the results of study through publication.

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