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Original Article

Gestational age, birth weight, and blood culture microbial patterns in late-onset neonatal sepsis

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Abstract

Background The three main causes of neonatal deaths in Indonesia according to the WHO are sepsis, prematurity, and asphyxia. A suboptimal hospital environment increases the risk of late-onset neonatal sepsis (LONS), which in turn can prolong hospital stays.
Objective To assess for possible associations of bacterial patterns in neonates with LONS, prematurity, and/or low birth weight.
Methods Medical record data of 1,706 hospitalized neonates who were treated for sepsis or other disease in the Neonatal Unit, Dr. Cipto Mangunkusumo Hospital (CMH), Jakarta in 2020 were analyzed retrospectively. A total of 262 neonates had proven LONS. We assessed for possible risk factors such as gestational age, birth weight, and cultured blood microbes.
Results Out of a total of 1,706 neonates admitted to the neonatal unit, the incidence of proven LONS was 15.4%. LONS was more prevalent (58.4%) in preterm than in full-term (41.6%) neonates. The majority (67.6%) of subjects with proven LONS were neonates with low birth weight (LBW) (<2,500 grams), and the largest percentage of them (35.1%) was in the 1,500-2,500 gram group. Gram negative bacteria emerged as the predominant pathogens of LONS patients in our hospital; the most common were *Klebsiella pneumonia, Acinetobacter spp., Escherichia coli, Enterobacter spp*., and *Pseudomonas aeruginosa*.
Conclusion The proportion of LONS among LBW and preterm neonates is significantly higher compared to normal birth weight and neonates. In our unit, LONS was mostly caused by Gram-negative bacteria. The antibiotic susceptibility of the various pathogens causing LONS in CMH should be tested and compared to the current empirical antibiotic guidelines used in CMH. **[Paediatr Indones. 2024;64:52-9; DOI: 10.14238/pi64.1.2024.52-9**].

Keywords: *late-onset neonatal sepsis; gestational age; birth weight; microbial pattern*

According to the *World Health Organization* (WHO), the three main causes of neonatal death in Indonesia are asphyxia, sepsis, and prematurity.[1] Neonatal sepsis is defined as systemic infection occurring in the first month of life.[2] The incidence rate of neonatal sepsis is 1 to 10 per 1,000 live births and up to 13-27 per 1,000 live births in very low birth weight infants.[2] The incidence of neonatal sepsis in each area and hospital may vary, with different risk factors.

Neonatal sepsis can be classified into two groups based on its timing. Early-onset neonatal sepsis (EONS) occurs within the first 72 hours of life, while late-onset neonatal sepsis (LONS) occurs after the age of three days.[3,4] The EONS is related to maternal infection in the prenatal period and during delivery, while LONS is related to an infection in the post-natal period during hospitalization.[5,6]

Birth weight is one of the determining factors for neonatal sepsis.[7] Neonates with low birth weight are

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at greater risk of sepsis.[8] Neonates with birth weights of <2,500 g were 1.42 times more likely to develop neonatal sepsis than neonates with birth weight 2,500 g and above. Preterm neonates were 3.36 times more likely to develop neonatal sepsis compared to neonates.[7]

LONS has been associated with exposure to hospital or community environments.[9] Gram-positive bacteria, namely coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, are currently the predominant pathogens responsible for neonatal LONS, followed by gram-negative bacteria and fungi. The proportions of the four main groups of pathogens do not substantially differ between preterm and term neonates. In very low birth weight (VLBW) and preterm infants, the majority of LONS was caused by Gram-positive bacteria (61.4%), followed by Gram-negative bacteria (26.2%), and candida (10.5%). Contamination rates are considered high in the neonatal intensive care unit (NICU), and blood specimens obtained from intravenous devices are more prone to be contaminated with CoNS.[10]

The Malaysian National Neonatal Registry reported that almost 50% of LONS cases in VLBW infants were caused by gram-negative bacteria. Approximately 50-70% of LONS cases in VLBW infants were caused by *Klebsiella spp., Enterobacter spp*., and *Escherichia spp*. The remaining 30%-50% of LONS cases were mainly attributed to *Pseudomonas spp., Serratia spp*., and *Acinetobacter spp*. *Klebsiella spp*. were shown to be responsible for almost half of LONS cases in an Israeli cohort of VLBW infants, while Escherichia spp. were reported to be the predominant pathogens for LONS in Canadian NICUs.[9] Jiang *et al.*[11] in China reported that the majority of LONS was caused by Gram-negative bacteria (51.8%), followed by Gram-positive bacteria (31.1%), and fungi (17.1%). *Klebsiella pneumoniae* was the most common pathogen for LONS. However, data on microbial patterns associated with prematurity and or low birth weight are lacking. Microbial patterns found in LONS may be similar or different from those in Indonesia. Therefore, we aimed to assess for possible associations between bacterial patterns in neonates with LONS, prematurity, and/or low birth weight.

Methods

This cross-sectional study was conducted in the Neonatal Unit of Cipto Mangunkusumo Hospital (CMH) using subjects' medical record data. We included neonates admitted to CMH from January to December 2020 with proven LONS based on blood culture results. We excluded neonates with incomplete medical record data.

Proven LONS was defined as sepsis occurring at or after 72 hours of life, with the presence of bacterial blood stream infection (bacteremia), confirmed by blood culture. Neonates were classified into term births (≥37 weeks) or preterm (<37 weeks). Preterm neonates were further classified by gestational age into extremely preterm (EP, <28 weeks), very preterm (VP, ≥28 to <32 weeks), or moderate to late preterm (MTLP, ≥ 32 to <37 weeks). The body weight of newborns at birth was classified into extremely low birth weight (ELBW, <1,000 g), very low birth weight (VLBW, ≥1,000 to <1,500 g), low birth weight (LBW, ≥1,500 to <2,500 g), or normal birth weight (NBW, ≥2,500 g).

We collected infants' demographic data from medical records, which included gestational age, birth weight, the presence of LONS, and mortality. The diagnosis of LONS was based on blood culture results obtained from the hospital's Clinical Pathology Laboratory. Data were collected and analyzed using *SPSS version 25* (*IBM*, Armonk, New York). This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Results

A total of 1,706 neonates were admitted with suspected LONS during the study period, of whom 262 neonates had proven LONS. The incidence of blood culture-proven LONS among those admitted in the NICU for suspected LONS was 15.4%. **Table 1** shows the demographic and clinical characteristics of neonates admitted with suspected LONS. Around 84.9% of the suspected LONS subjects were 'inborn,' meaning that they were born at CMH; the rest were 'outborn', meaning that they were born elsewhere and referred to CMH.

Out of the 262 neonates with proven LONS, 151

were inborn (57.6%) and 111 were outborn (42.4%). Among the proven LONS subjects, the number of males (56.3%) was higher than the number of females (43.7%). Proven LONS was more prevalent in preterm (58.4%) than in term neonates (41.6%). Most inborn subjects were preterm, while most outborn subjects were term neonates. The majority of subjects with proven LONS (67.6%) had birth weights of <2,500 grams, and the largest proportion of these (35.1%) were classified as LBW (**Table 2**).

Table 1. Characteristics of neonates admitted to the NICU with suspected LONS

Characteristics	(N=1,706)
Gender, n (%)	
Male	886 (51.9)
Female	812 (47.8)
Ambiguous	8 (0.4)
Gestational age, n (%)	
EP	61 (3.5)
VP	152 (8.9)
MTLP	477 (27.9)
Full term	1,016 (59.5)
Birth weight, n (%)	
ELBW	81 (4.7)
VLBW	165 (9.6)
LBW	542 (31.7)
NBW	918 (54.0)
Neonatal admissions, n (%)	
Inborn	1,450 (84.9)
Outborn	256 (15.0)
LONS, n (%)	
Proven	262 (15.4)
Unproven	1,444 (84.6)

Table 3 shows the types of pathogenic microbes grown from blood cultures of proven LONS patients. Gram negative bacteria emerged as the predominant pathogens of LONS at CMH during the study period. The most common Gram-negative bacteria found were *Klebsiella pneumonia, Acinetobacter spp., Escherichia coli, Enterobacter spp*., and *Pseudomonas aeruginosa*. Among Gram-positive bacteria, the most common pathogens were methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus saprophyticus* (MRSS), *Staphylococcus aureus*, and *Staphylococcus saprophyticus*. Among fungal cases, candida infections were the most common, including *Candida parapsilosis, Candida albicans, Candida famata, Candida guillermondi*, and *Candida tropicalis*.

As shown in **Table 4**, there were more males than females with proven LONS (57.2% *vs.* 42.7%, respectively). Proven LONS was more common among preterm compared to term neonates (P<0.005). In addition, there was a significantly greater proportion of LBW than NBW neonates with proven LONS (P<0.005). There were significantly more inborn neonates with proven LONS than outborn neonates (P<0.005).

As presented in **Table 5**, Gram negative bacteria were the predominant cause of LONS in all groups. Gestational age (P=0.001), birth weight (P=0.012), and inborn or outborn nature of admission (P=0.013) were strongly associated with microbial pattern.

Table 2. Characteristics of proven LONS patients by nature of admission

Characteristics	Inborn (n=151)	Outborn (n=111)	Total (N=262)
Gender, n (%)			
Male	85 (56.3)	66 (59.5)	151 (57.6)
Female	66 (43.7)	45 (40.5)	111 (42.4)
Gestational age, n (%)			
EP	15 (9.9)	1 (0.9)	16 (6.1)
VP	65 (43.0)	7 (6.3)	72 (27.5)
MTLP	40 (26.5)	25 (22.5)	65 (24.8)
Full term	31 (20.5)	78 (70.3)	109 (41.6)
Birth weight, n (%)			
ELBW	24 (15.9)	4 (3.6)	28 (10.7)
VLBW	43 (28.5)	14 (12.6)	57 (21.8)
LBW	57 (37.7)	35 (31.5)	92 (35.1)
NBW	27 (17.9)	58 (52.3)	85(32.4)

Table 3. Pathogens found in neonates with proven LONS (N=262)

Variables	No. of subjects
Gram positive	**163**
Enterococcus faecalis	0
Staphylococcus aureus	28
Staphylococcus epidermidis	45
Staphylococcus epidermidis (MRSE)	47
Staphylococcus haemolyticus	1
Staphylococcus saprophyticus	6
Staphylococcus saprophyticus (MRSS)	36
Streptococcus alphahemolytic	0
Gram negative	**300**
Acinetobacter spp.	57
Acinetobacter baumannii	3
Aeromonas hydrophila	1
Aeromonas salmonicida	2
Burkholderia cepacian	0
Citrobacter koseri	1
Elizabethkingia meningoseptica	1
Escherichia coli	34
Enterobacter spp.	32
Enterobacter cloacae	7
Enterobacter aerogenes	8
Klebsiella oxytoca	1
Klebsiella pneumoniae	113
Leclercia adecarboxylata	1
Proteus mirabilis	4
Pseudomonas aeruginosa	31
Salmonella sp	1
Serratia marcescens	1
Stenotrophomonas maltophilia	2
Fungi	**41**
Candida sp	9
Candida albicans	7
Candida ciferrii	2
Candida famata	4
Candida guilliermondi	4
Candida lusitaniae	3
Candida parapsilosis	5
Candida pelliculosa	2
Candida tropicalis	3
Kodamaea ohmeri	2

Discussion

In our study, proven LONS was more common in preterm (58.4%) than in term (41.6%) neonates (P<0.005). The incidence of LONS was also significantly higher in LBW (67.6%) than in NBW neonates (32.4%) (P<0.005). Similarly, previous studies reported that the risk of LONS was higher in LBW and preterm neonates.[12,13] Preterm babies have immature immune systems and LBW babies are mostly preterm. They may need invasive medical interventions such as intravascular access or mechanical ventilation, which are known ports of entry to pathogens that can cause bacteremia.[13]

The overall incidence of blood culture-proven LONS in inborn neonates was 10.5%, while in outborn neonates it was as high as 43% (P<0.005). CMH is the top national referral hospital in Indonesia, typically receiving patients with severe, complicated conditions. Pregnant women are referred to give birth in CMH because of maternal risk factors such as premature rupture of membranes (PROM), infections, or the presence of congenital anomalies in the fetus. As a consequence, neonates born in CMH are likely to have comorbidities, putting them at higher risk of LONS. On the other hand, outborn neonates are commonly referred to CMH due to the presence of congenital malformations detected postnatally or when they are generally unwell and need more advanced treatment. Due to the lengthy referral process, such neonates often arrive in CMH with devastating conditions (e.g., severe sepsis). Some factors contributing to the delayed arrival at CMH are lack of proper transportation, long and complicated referral processes, and the hospital's limited capacity. Only around 65.8% of the primary healthcare centers in Indonesia have transportation for referring patients.[14] Full-term neonates referred to CMH might acquire LONS because of their comorbidities, such as severe asphyxia requiring mechanical ventilation, intrauterine growth restriction, or congenital malformations that require surgery. The presence of comorbidities puts these neonates at risk of having to undergo surgery and/or invasive medical interventions, thereby prolonging the duration of hospitalization, and increasing the risk of LONS.[15]

Gram-negative bacteria (49.2%) were more commonly found to be the cause of LONS in CMH

Table 4. Analysis of LONS with gestational age and birth weight

Variables	Proven LONS (n=262)	Unproven LONS (n=1,444)	P value
Gender, n (%)			
Male	150 (57.2)	736 (51.0)	0.098
Female	112 (42.7)	700 (48.5)	
Ambiguous	0	8 (0.5)	
Gestational age, n (%)			
<28 weeks	18 (6.9)	43 (4.8)	<0.005
28-31 weeks	54 (20.6)	98 (6.8)	
32-36 weeks	80 (30.5)	397 (27.5)	
>37 weeks	110 (42.0)	906 (62.7)	
Birth weight, n (%)			
<1000 g	29 (11.1)	52 (3.6)	<0.005
1000-1499 g	57 (21.8)	109 (7.5)	
1500-2499 g	96 (36.6)	450 (31.2)	
>2500 g	80 (30.5)	833 (57.7)	
Neonatal admission, n (%)			
Inborn	151 (57.6)	1,298 (89.9)	<0.005
Outborn	111 (42.4)	146 (10.1)	

Table 5. The association between patient demographics and microbial pattern

Variables	Gram positive (n=55)	Gram negative (n=129)	Mixed (n=78)	P value
Gender, n (%)				
Male	35 (23.4)	69 (46)	46 (30.6)	0.415
Female	20 (17.8)	60 (53.6)	32 (28.6)	
Gestational age, n (%)				
Preterm	44 (29)	64 (42.1)	44 (28.9)	0.001
Full term	11 (10)	65 (59.1)	34 (30.9)	
Birth weight, n (%)				
LBW	47 (25.8)	82 (45.1)	53 (28.8)	0.012
NBW	8 (10)	47 (58.8)	25 (31.2)	
Neonatal admission, n (%)				
Inborn	41 (27.2)	72 (47.7)	38 (25.2)	0.013
Outborn	14 (12.6)	57 (51.4)	40 (36)	

than gram positive bacteria (20.1%) or mixed infection (29.8%). Significant differences in microbial pattern were found between preterm and term (P=0.001), LBW and NBW (P=0.012), as well as between inborn and outborn (P=0.013) neonates. *Klebsiella pneumoniae* was the most common etiology, followed by *Acinetobacter spp*. Our results were in agreement with a systematic review in 2021 which reported that 60% of neonatal sepsis cases were caused by gram negative bacteria (60%), with *Klebsiella spp.* as the most common pathogen, followed by *Acinetobacter spp*. in the Asian region.[16]

Transmission of *K. pneumoniae* between patients in neonatal care units is facilitated by the hands of healthcare staff. *K. pneumoniae* has the ability to reproduce on surfaces and colonize the skin, intestines, as well as the genitourinary and respiratory tracts. A study in Italy concluded that outbreaks of *K. pneumoniae* in the neonatal unit are possible if hygiene measures are decreased.[17] In addition, Gram-negative bacterial infections are also associated with use of central venous catheters.[16]

K. pneumoniae is also known to cause a higher frequency of medical complications such as acute respiratory failure, intraventricular hemorrhage, and bronchopulmonary dysplasia in LONS compared to EONS. In addition, *K. pneumoniae* is often resistant to penicillin, beta-lactams, and cephalosporins. It is still sensitive to ciprofloxacin, amikacin, and levofloxacin.[18]

Acinetobacter species, specifically *Acinetobacter baumannii*, have been reported to be a dominant cause of neonatal sepsis in preterm and LBW neonates. The same study also showed that acinetobacter species in neonatal sepsis are mostly multi-drug resistant strains (95.9%), with the majority of specimens resistant to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides. However, all specimens were still sensitive to colistin.[19] A study reported significant risk factors for acinetobacter infection in neonates, which included hospital birth, LBW (<1,500g), preterm birth, mechanical ventilation, and hospitalization >7 days. The use of central venous catheters, age of <7 days, and incubator care were not statistically significant.[20]

Gram-positive bacteremia was found in 20.1% of our subjects. Coagulase-negative staphylococci (CoNS), such as *S. epidermidis, S. saprophyticus*, and *S. haemolyticus*, were the main pathogens causing LONS. Of cases with Gram-positive bacteremia, 82.2% were caused by CoNS, with MRSE and *S. epidermidis* being the two most common. Similar results were reported in a previous study which stated that nearly 50% of LONS cases were caused by CoNS.[21] Coagulase-negative staphylococci are a major component of skin normal flora, and *S. epidermidis* can also be found in mucous membranes of the nasopharynx. *S. epidermidis* and *S. haemolyticus* are known to cause blood infections in neonates, entering the bloodstream through injured skin. Thus, transmission to susceptible neonates is facilitated by invasive medical interventions, such as intravenous access, mechanical ventilation, and central venous catheter insertion.[21]

A study also found that 50.9% of Gram-positive bacteria in LONS cases were *Staphylococcus epidermidis* (MRSE) and *Staphylococcus saprophyticus* (MRSS). These pathogenic strains can produce biofilms, when colonizing their hosts. These strains are known to be multidrug-resistant in NICU settings.[22]

Although only 14.9% of subjects had *Candida spp*. infection in our study, is it is worth noting that candidemia may cause significant long-term effects on patients such as blindness, hearing impairment, cerebral palsy, and periventricular leukomalacia.[23] Fungal infection is also associated with a higher mortality rate.[24,25] We found that *Candida albicans* was responsible for 7 of 41 fungal blood isolates, while the remaining 33 fungal blood isolates were caused by non-albicans species. This finding was in accordance with a systematic review, which reported that non-albicans species were more common in Asian countries.[7]

The number of LBW neonates with LONS was significantly higher (67.6%) than NBW neonates (32.4%) (P<0.005). This finding was in agreement with a previous report that LBW infants have increased risk of developing LONS. They are at higher risk of LONS because they are often premature, unable to feed, have immature thermoregulation systems, and are more likely to experience hypoglycemia.[26] Fetal growth restriction also causes LBW, as these infants are usually born at >37 weeks. These neonates have higher risk of multiple complications, including sepsis, increased need for respiratory support, delayed enteral feeding, prolonged NICU stay, and necrotizing enterocolitis.[26]

In conclusion, the incidence of LONS in the Neonatal Unit, CMH in 2020 was 15.4%. The most common causative Gram-negative bacteria were *Klebsiella pneumonia, Acinetobacter spp., Enterobacter spp., Escherichia coli*, and *Pseudomonas aeruginosa,* while the most common Gram-positive bacteria were MRSE, MRSS, and *Staphylococcus aureus*. Factors associated with LONS are LBW and prematurity. Birth weight, gestational age, and inborn or outborn nature of admission are significantly associated with microbial pattern. LONS was mostly caused by Gram-negative bacteria regardless of birth weight and gestational age.

Conflict of interest

None declared.

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