GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

Check for updates

Characteristics of neonatal late onset sepsis in Sanglah Hospital, Bali

Arya Wisnu Prayoga *, Made Kardana, I Wayan Dharma Artana, Putu Junara Putra and Made Sukmawati

Department of Child Health, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia.

GSC Advanced Research and Reviews, 2021, 07(02), 073–082

Publication history: Received on 08 April 2021; revised on 10 May 2021; accepted on 13 May 2021

Article DOI: https://doi.org/10.30574/gscarr.2021.7.2.0105

Abstract

Neonatal Late-Onset Sepsis (LOS) is a leading cause of mortality in the Neonatal Intensive Care Unit (NICU). The microbial characteristics of LOS are of primary importance in guiding clinical antisepsis practice, and strategies to prevent and treat neonatal LOS, in turn, influence the pattern of LOS pathogens. This study is a retrospective descriptive study with a cross-sectional approach conducted between 2016 until 2020 in the neonatal ward (level II-III) of the Sanglah General Hospital, Bali. Data collected consists of demography, clinical characteristics, laboratory results, and outcomes. Subjects in this study dominated by male (64%), gestational age > 37 weeks (56%), born ≥ 2.500 grams (54%), last mother education mostly in Senior High School (56%), spontaneous delivery method (54%) and 31 (62%) subjects were referral from other hospital and primary health care. Most of the subjects were lethargic (68%) and 15 (30%) subjects were died. Laboratory finding normal leukocyte, neutrophil, lymphocyte, hemoglobin, thrombocyte and IT ratio but have higher procalcitonin result. Poor outcome group were dominated by male, smaller gestational age, VLBW, and neonates who experience lethargy, temperature instability, respiratory distress and got positive blood culture.

Keywords: Neonatal late-onset sepsis; Characteristics; Laboratory; Outcome

1. Introduction

Neonatal late-onset sepsis (LOS), defined as sepsis onset after 72 hours of life in neonatal period, is a leading cause of mortality in the neonatal intensive care unit (NICU) [1]. The incidence rates for LOS in preterm infants vary between 20 and 38% in the first 120 days of life, and mortality rates range from 13 to 19% [1]. Survivors are at risk for prolonged hospitalization, development of Necrotizing Enterocolitis (NEC), bronchopulmonary dysplasia, and neurodevelopmental impairment [1-3].

The diagnosis of neonatal LOS in daily clinical practice may be challenging, especially in preterm infants, as clinical symptoms have limited sensitivity and specificity. The gold standard for diagnosis is confirmation of a pathogen in the blood culture, which is limited by suboptimal sensitivity and delay of a definite diagnosis because of the turnaround time to become positive. In addition, screening of bodily fluids (e.g., blood and urine) may also require an invasive procedure, increasing the risk for LOS independently [4].

Meanwhile, the incidence of neonatal LOS in china was 4.4%. LOS has increased in parallel with the improved survival of premature infants, especially in those with Very Low Birth Weight (VLBW), indicating the role of hospitalization and life sustaining medical devices in the pathogenesis of neonatal LOS. The microbial characteristics of LOS are of primary importance in guiding clinical antisepsis practice, and strategies to prevent and treat neonatal LOS, in turn, influence the pattern of LOS pathogens [5, 6]. An up-to-date and thorough understanding of the characteristic and management of neonatal LOS may help to reduce the burden of this disease.

* Corresponding author: Arya Wisnu Prayoga
Department of Child Health, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia.

2. Material and methods

2.1. Design and Sample

This study is a retrospective descriptive study with a cross-sectional approach conducted between 2016 until 2020 in the neonatal ward (level II-III) of the Sanglah General Hospital, Bali. Sampling was done by purposive sampling. The inclusion criteria are neonates who are treated with neonatal LOS with the exclusion criteria is incomplete data. The basic data of study subjects were obtained from registers and medical records. Total samples in this study were 50 patients.

This study was approved by the Ethics Committee of Sanglah Hospital, Denpasar, Bali.

2.2. Operational definitions of variables

Clinically late-onset neonatal sepsis is a clinical syndrome in the form of at least 1 clinical symptom of sepsis neonatorum based on:

- General condition: Not doing well, poor fed, hyperthermia, hypothermia, sclerema, edema,
- Central nervous system: Hypotonia, lethargy, seizure, irritable, high pitched cry,
- Respiratory system: Apnea, tachypnea, dyspnea, cyanosis, irregular breathing,
- Cardiovascular system: Tachycardia, bradycardia, clammy, shock,
- Gastrointestinal system: Retention, hepatomegaly, diarrhea, vomiting, meteriomus.
- Sepsis definition based on laboratory test: Positive blood culture result, leukopenia (total leukocyte count < 5.000/pl), leukocytosis (total leukocyte count > 30.000/pl), thrombocytopenia (platelet count < 150.000/u]), increase of immature to total neutrophil ratio (I/T ratio) >0.2, or increased serum CRP. Infection occurs due to infection arising more than 72 hours after birth.

2.3. Data Analysis

The collected data is processed using SPSS 22.0 software to describe the characteristics of the studied variables. Categorical variables are described in the number (n) and percentage (%). Continues data will be presented in mean and deviation standard if normally distributed, or median and range if not normally distributed. Data that has been processed is presented in the tables and narration.

3. Results

During 2016 – 2020, we identified 50 cases neonates with LOS that included in this retrospective descriptive study from Sanglah Hospital. Data collected consists of demography, clinical characteristics, laboratory results, and outcomes. Subjects in this study dominated by the male (64%) with gestational age > 37 weeks (56%). There were 27 (54%) born ≥ 2.500 grams. Most of subjects were NBW (54%). The median age of our subjects is 11.46 days old. Last mother education mostly in Senior High School (56%). Most of our subjects have spontaneous delivery method (54%) and 31 (62%) subjects were referral from other hospital and primary health care. Patient demographic were listed in Table 1.

Table 1 Characteristic Demography

Variables	**N = 50**
Age[a] (day)	11.46 (3 – 25)
Gestational age[b]	
< 37 weeks	22 (44)
≥ 37 weeks	28 (56)
Gender[b]	
Male	32 (64)
Female	18 (36)
Birth weight[b]	

< 1.000 gram (ELBW)	0 (0)
1.000 – 1.499 gram (VLBW)	8 (16)
1.500 – 2.499 gram (LBW)	15 (30)
≥ 2.500 gram (NBW)	27 (54)
Mother Education	
Elementary school	4 (8)
Junior High School	12 (24)
Senior High school	28 (56)
Bachelor	6 (12)
Delivery Method	
Spontaneus	27 (54)
Sectio Caesaria	23 (46)
Referral	
Yes	31 (62)
No	19 (38)
Maternal Age	
<35 years old	34 (62)
≥35 years old	16 (32)

[a]: Median (min – max value); [b]: n (%)

Extremely low birth weight babies (ELBW); Very low birth weight babies (VLBW); Low birth weight babies (LBW); Normal birth weight babies.

Table 2 shows characteristics of clinical manifestation in subjects. Most of the subjects were lethargic (68%), experience respiratory distress (28%), have meningitis neonatal (28%) only a few of them have temperature instability (4%), diarrhea neonatal (8%), seizure (4%) and 15 subjects were died (30%).

Table 2 Characteristic clinical subjects

Variables	**n (%)**
Diarrhea Neonatal	
Yes	4 (8)
No	46 (92)
Lethargy	
Yes	34 (68)
No	16 (32)
Temperature instability	
Yes	2 (4)
No	48 (96)
Seizure	
Yes	2 (4)
No	48 (96)
Respiratory distress	

Yes	14 (28)
No	36 (72)
Meningitis Neonatal	
Yes	14 (28)
No	36 (72)
Outcome	
Life	35 (70)
Death	15 (30)

Table 3 Characteristic of laboratory results

Variables	**N = 50**
Blood panel	
Leukocyte (10^3/µL)[a]	12.58 (2.15 – 44.72)
Neutrophil (10^3/µL)[a]	5.58 (0.65 – 31.99)
Lymphocyte (10^3/µL)[b]	4.08 (2.33)
Hemoglobin (g/dL)[b]	15.01 (3.26)
Thromobocyte (10^3/µL)[b]	241.277 (141)
IT Ratio[a]	0.18 (0.01 – 1.06)
Procalcitonin (ng/mL)[a]	0.94 (0.1-167.2)
Vacuolization [c]	
Positive	19 (38)
Negative	31 (62)
Toxic granule [c]	
Positive	9 (18)
Negative	41 (82)
Blood culture [c]	
No Growth	40 (80)
Growth	10 (20)

[a:] Median (min-max value); [b:] Mean (standard deviation); [c:] n (%)

Table 3 shows characteristics of laboratory results which consist of a blood panel, the presence of vacuolization, toxic granule, and blood culture. Most of the subjects had normal leukocyte count with median 12.58 × 10^3/µL. The median value of neutrophil is 5.58 × 10^3/µL and mean of lymphocyte is 4.08 × 10^3/µL. Hemoglobin and/thrombocyte level within the normal limit. IT ratio appears high in most subjects with median 0.18 (range 0.01 – 1.06). Procalcitonin median is 0.94 (range 0.1-167.2).

Table 4 Comparison of demography, clinical profiles and subject outcomes.

Variables	Life n(%)	Death n(%)
Gestational age		
< 37 weeks	14 (40)	8 (53.3)
≥ 37 weeks	21 (60)	7 (46.7)
Gender		
Male	23 (65.7)	9 (60)
Female	12 (34.3)	6 (40)
Birth weight		
< 1.000	0 (0)	0 (0)
1.000– 1.499	4 (11.4)	4 (26.7)
1.500 – 2.499	11 (31.4)	4 (26.7)
≥ 2.500	20 (57.2)	7 (46.6)
Mother education		
Elementary school	4 (11.4)	0 (0)
Junior High School	9 (25.7)	7 (46.7)
Senior High school	20 (57.2)	8 (53.3)
Bachelor	2 (5.7)	0 (0)
Delivery method		
Spontaneus	20 (57.2)	7 (46.7)
Sectio Caesaria	15 (42.8)	8 (53.3)
Referral		
Yes	19 (54.3)	12 (80)
No	16 (45.7)	3 (20)
Maternal Age		
<35 years old	28 (80)	6 (40)
≥35 years old	7 (20)	9 (60)
Meningitis neonatal		
Yes	14 (40)	0 (0)
No	21 (60)	15 (100)
Diarrhea neonatal		
Yes	3 (8.6)	1 (6.7)
No	32 (91.4)	14 (93.3)
Lethargy		
Yes	24 (68.6)	10 (66.7)
No	11 (31.4)	5 (33.3)
Temperature instability		
Yes	1 (2.9)	1 (6.7)
No	34 (97.1)	14 (93.3)
Seizure		
Yes	1 (2.9)	1 (6.7)
No	34 (97.1)	14 (93.3)
Respiratory distress		
Yes	11 (31.4)	3 (20)
No	24 (68.6)	12 (80)

Table 5 Comparison of laboratories profiles and subject outcomes

Variables	Life n(%)	Death n(%)
Blood panel		
Leukocyte (10^3/µL)[a]	11.74 (5.3-44.72)	16.01 (2.15-29.85)
Neutrophil (10^3/µL)[a]	5.13 (0.8-31.99)	7.08 (0.65-24.01)
Lymphocyte (10^3/µL)[b]	4.6 (2.28)	2.9 (2.08)
Hemoglobin (g/dL)[b]	15.4 (3.41)	14.1 (2.79)
Thromobocyte (10^3/µL)[b]	260.6 (151)	196.1 (107)
IT Ratio[a]	0.18 (0.01-1.06)	0.28 (0.02-1.05)
Procalcitonin (ng/mL)[a]	0.66 (0.11-73.99)	7.59 (0.18-167.2)
Vacuolization[c]		
Positive	13 (37.1)	6 (40)
Negative	22 (62.9)	9 (60)
Toxic granule[c]		
Positive	7 (20)	2 (13.3)
Negative	28 (80)	13 (86.7)
Blood Culture[c]		
Positive	4 (11.4)	6 (40)
Negative	31 (88.6)	9 (60)

[a]: Median (min-max value); [b]: Mean (standard deviation); [c]: n (%)

The outcome for subject's characteristics shows in Table 4. Most of the passed away subjects were male, birth weight above 2.500 grams, term, and showed lethargy. The subject outcome for each laboratory's characteristic shows in Table 5. Most of the passed away subjects had higher procalcitonin level, and 6 subjects (40%) were died with positive blood culture.

4. Discussion

Newborns or in neonatal period are especially vulnerable to infection. Late onset sepsis is more frequent in the neonatal period than in any other time of life and leads to a high incidence of mortality and long-term neurological sequels, particularly those born of very low birth weight and preterm. The cellular and humoral immunities are immature, including the phagocytic function. A full-term newborn has a distinct innate immune system that is biased towards T-helper type 2/T-helper type 17-polarizing and anti-inflammatory cytokine production, with relative impairment in T-helper type 1-polarizing and cytokine production. It is widely believed that the development of the blood–brain barrier (BBB) proceeds from late gestation and continues through the postnatal period, and it may be a time of increased permeability that renders the developing brain more vulnerable. Immature and very low birth weight newborns have improved survival but remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections [7, 9]. In our study showed that the neonatal LOS were mostly aterm (>37 gestational age) (64%). It was different from Umate et al. (76.9%) that report high incidence in preterm. The result was different caused by early diagnosed for preterm babies. Most of preterm babies diagnosed by suspected early onset sepsis and got proper antibiotic till blood culture came out, beside that most of our subjects is aterm baby.

There is a gender–linked susceptibility to neonatal LOS, in which male is more prone to develop neonatal meningitis. Similar sex discrepancy in neonatal LOS is found in other countries. Though the exact reason for this male preponderance is not known with certainty, it is probably due to the fact that the factors regulating the synthesis of globulins are situated on the X chromosome. Since the male has only one X chromosome, male is less immunologically protected than the females. The other reasons may be related to underlying development processes, including those

affecting the immune, endocrine, and reproductive systems, or differences in reporting rates [6-8]. In our study we found that neonatal LOS is found predominantly in male (64%) compared to female (36%). This finding is similar with several studies such as Jiang et al. (55.1%) and Hammoud et al. (52%).

Most VLBW neonates have complicated medical problems and prolonged hospitalization. The association between low birth weight and neonatal LOS could be explained by an immature immune system or greater exposure to other risk factors [2, 9-11]. But in our study found that most of neonatal developing meningitis was born with weight > 2.500 grams (54%), subjects in which VLBW (16%) experience 50% death. This finding different from any journal, caused by determining early diagnosis, LBW baby with sepsis symptom, always suspected with early onset sepsis and got antibiotics till blood culture comes out.

Low educated mother was one of risk factor of neonatal LOS, late of referral and neglected patients were the main problem in outcome neonatal LOS patients. In this study, almost all of the subject's mothers got well educated. For the outcome, most of died subjects had junior high school and senior high school mother education, neither bachelor mother had no died subjects. This finding also similar with Husada et al. was found low educated mother were risk factor of neonatal LOS (78%) [12].

Obstetric risk factors are very important for distinguishing the origin of neonatal infection. Many bacteria can promote sepsis in infants up to three months and neonatal period. Infection by bacteria may be arising out of childbirth due to vagina mucosa because those are pathogens that colonize the region. Guo et al. concluded that vaginal delivery and low birth weight were the risk factors for infection and supported by data in which 59% of their subjects were born spontaneously. That study is in accordance with our study which found that 54% of subjects were born spontaneously. Frequent digital vaginal examination and duration of labour also increased the risk of neonatal sepsis and meningitis. Newborn infection that is the result of passage through the birth canal is considered nosocomial and no specific time during or after hospitalization is given to determine whether an infection is nosocomial [13].

Maternal age is significantly associated with adverse obstetrical outcomes like pregnancy-induced hypertension and antepartum haemorrhage. Caesarean delivery was also tremendously increased in those mothers. On top of this, advanced maternal age pregnancy was also found to be a major risk factor for preterm delivery, low birth-weight, low fifth minute APGAR score and perinatal death. Our study shows advanced maternal age induced high risk of death outcomes. These findings also similar with Mehari et al. that shows advanced maternal age have 4x risk of preterm babies [11, 13].

The initial clinical manifestations of neonatal LOS may present with one or more of the following symptoms and signs: (a) hypothermia or fever (former is more common in preterm low birth weight infants), (b) lethargy, poor cry, refusal to suck, (c) poor perfusion, prolonged capillary refill time, (d) hypotonia, absent of neonatal reflexes, (e) brady/tachycardia, (f) respiratory distress, apnea, and gasping respiration, (g) hypo/hyperglycaemia, (h) diarrhoea, and (i) metabolic acidosis Specific features related to various systems like the central nervous system is, seizure. The presence of these features should raise clinical suspicion of neonatal LOS. In our study, we found respiratory distress (28%) and lethargy (68%) as the most clinical features from our subjects. This finding also similar with Bhagat et al. with the most clinical findings in neonatal LOS was lethargic (100%) and respiratory distress (58.5%). In addition Umate et al. was found lethargic (68.75%) and respiratory distress (72.60%). Temperature instability and seizure also found as independent factors associated with serious CNS complication [12-14]. That statement is strengthened by our results in which there was no temperature instability (96%) neither seizure (96%) most of our subjects had good outcome (70%).

Neonatal LOS is due to organisms acquired after delivery from nosocomial or community sources. Neonatal meningitis is a serious consequence of LOS. In the past decade, the mortality rate usually is lower than that for early-onset sepsis but can vary between 2% and 40% in most neonatal care facilities, with a mortality of 33%–48% in developing countries [7, 13-14]. Meningitis neonatal occurs due to hematogenous spread and is sequelae of bacteremia have been associated with systemic bacterial infections during the first month of life. As bacteremia complications are common in late onset sepsis, and meningitis is frequent among late onset sepsis cases [15]. In our study we found that the prevalence of meningitis neonatal occurs in neonatal sepsis (28%) with mean age of our subjects is 11.46 days old. This observation was consistent with Ismael et al (77.78%). The mean age of neonatal meningitis consistent with Barichello et al. which occurs at 4–5 weeks of age (range: 7–89 days) [16].

Peripheral blood smears White Blood Cell (WBC) count < 5.000/mm^3 and > 20.000/mm^3, with absolute neutrophil count of less than 1.800 cells/cu mm were accepted as pathologic. The WBC upper limit is set at 30.000 – 40.000/mm^3 in many sepsis screenings protocols. However, it is noteworthy that leucocytosis was not detected in one-third of cases

diagnosed with sepsis. Although the normal value of WBC has a very wide range, it can be affected by the time and place of collection of the sample, the gestational week of the baby, and factors other than sepsis. We found WBC median level about 12.58 (range 2.15 – 44.72) x 10^3/µL. This finding similar with Macias-Parra et al., they found peripheral WBC level was 11.6 (1.5 - 42.05) x 10^3/µL. From this finding it was states that the peripheral WBC count was neither sensitive nor specific for neonatal LOS. The IT ratio and counts have highest sensitivity. The IT ratio in uninfected neonates was accepted as 0.16 in the first 24 hours, decreasing to 0.12 by 60 hours. The upper limit for neonates at 32 weeks' gestation or less was slightly higher which is 0.2. IT ratio of more than 0.2 was considered as a case of sepsis. Procalcitonin more than 0.45 was considered as a case of sepsis [3, 17-18]. In our study, we found IT ratio mean is about 0.5 with range 0.01 – 11. Our study is similar with Ismael et al that found IT ratio mean 0.17, with range about 0.09 - 0.33, procalcitonin median is 0.94 (0.1-167.2). Our study also found median leukocyte 12.58 x 10^3/µL (2.15– 44.72), neutrophil 5.58 x 10^3/µL (0.65 – 31.99), normal lymphocyte 4.08 x 10^3/µL (2.33). Hemoglobin found 15.01% (3.26), platelet count was found 241.277/mm^3 (141.000/mm^3). Our finding similar with Macias-Parra., et al with median hemoglobin 14.1 g/dL and thrombocyte count was 203 (range 2 – 800 x 10^3/µL) [19-21].

Due to its weak positive and negative predictive value, the benefit of the use of complete blood count as a biomarker in neonatal sepsis and neonatal meningitis has not been proven. High or low WBC, high absolute neutrophil counts, high IT ratio, high procalcitonin and low platelet counts are associated with neonatal LOS. In accordance with our result, systemic bacterial infection may lead to malfunctions of the hemopoietic system. Whereas complete blood count is often used in conjunction with blood culture data to determine neonatal LOS. The association of elevation of white cell count, absolute neutrophil count and band neutrophil count with acute infectious diseases has been documented for decades [19].

Recently, it was reported that morphologic change in neutrophils could be helpful in predicting acute bacterial infections. The morphologic characteristics included the presence of toxic granulations and toxic vacuolations in neutrophils. In our study, we found presence of vacuolization about 38% and toxic granule about 18%. Of these, the presence of toxic granulations was demonstrated to have a predictive role in acute bacterial infections, while the relationship between bacterial infections and vacuolated neutrophils remains controversial. Overall, severe bacterial infections should be watched out in the consistent presence of leukocytosis with predominant neutrophilia, as well as the morphologic changes in neutrophils, such as toxic granulations, and toxic vacuolations [19, 21].

Blood culture is the gold standard for the diagnosis of neonatal sepsis. However, its positivity rate is low and is affected by blood volume inoculated, prenatal antibiotic use, and level of bacteraemia and laboratory capabilities. In developing countries, culture-negative sepsis is responsible for the majority of episodes. Currently, the recommended minimal blood volume for cultures in newborns is 1 ml, but most samples taken are of less than 0.5 ml. One classic study, focusing on E. coli infection, found that neonates have high-colony-count bacteraemia. However, a more recent study including other common neonatal-sepsis pathogens found that 68% of septic infants have low-level bacteremia (≤10 Colony-forming units (CFU)/ml) and 42% have counts ≤1 CFU/ml.20 In low colony count bacteraemia, as many as 60% of cultures will be falsely negative with 0.5 ml sample volumes. Multiple blood cultures could help increase the yield of this test, but studies in the neonatal period have shown conflicting results [22]. In our study, we found presence of positive blood culture about 20%, 6 subjects experience death with positive blood culture (60%). Three subjects have 2 blood culture positive result at hospitalization. Blood culture was do multiple caused by clinically and laboratories worsen. All of them were died.

5. Conclusion

The characteristic of neonatal LOS in our center was dominated by male and normal birth weight. Most of the subjects were lethargic and some of them experience respiratory distress. Our subjects also tend to have normal leukocyte, neutrophil, lymphocyte, haemoglobin, thrombocyte and IT ratio but have higher procalcitonin result. Poor outcome group were dominated by male, smaller gestational age, VLBW, and neonates who experience lethargy, temperature instability, respiratory distress and got positive blood culture.

This study is not analysing the relationship between profiles and outcomes so that they cannot describe the predictor factors. Further research is needed to look at the predictor factors affecting LOS outcomes treated at the neonatal ward.

Compliance with ethical standards

Acknowledgments

The author is thankful to the Department of Child Health, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia for providing facility for this study.

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Qazi SA, Stoll BJ. Neonatal sepsis: A major global public health challenge. Pediatr Infect Dis J. 2009; 28: 1–2.

[2] Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotton CM, et al. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr. 2013; 162: 1120–4.

[3] Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011; 96: 9–14.

[4] Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, et al. Incidence, clinical characteristics, and risk factors for adverse outcome in neonates with late onset sepsis. Pediatr Infect Dis J. 2014; 33: 7–13.

[5] Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics. 2005; 116: 595–602.

[6] Shim GH, Kim SD, Kim HS, Kim ES, Lee HJ, Lee JA, et al. Trends in epidemiology of neonatal sepsis in a tertiary center in Korea: a 26-year longitudinal analysis, 1980–2005. J Korean Med Sci. 2011; 26: 284–9.

[7] Jiang S, Yang C, Yang C, Yang Y, Cao Y. Epidemiology and microbiology of late-onset sepsis among preterm infants in China, 2015–2018: A cohort study. / International Journal of Infectious Diseases. 2020; 96: 1–9.

[8] Hammoud MS, Al-Taiar A, Thalib L, Al-Sweih N, Pathan S, Isaacs D. Incidence, aetiology and resistance of late-onset neonatal sepsis: a five-year prospective study. J Paediatr Child Health. 2012; 48: 604–9.

[9] Umate S, Garg BD, Kabra NS. Incidence of meningitis in neonates with late-onset sepsis at a Tertiary Care Center in Western India: An observational study. J Clin Neonatol. 2019; 8: 67-70.

[10] Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology. 2010; 97: 22–8.

[11] Mehari M, Maeruf H, Robles CC, Woldemariam S, Adhena T, Mulugeta M, et al. Advanced maternal age pregnancy and its adverse obstetrical and perinatal outcomes in Ayder comprehensive specialized hospital, Northern Ethiopia, 2017: a comparative cross-sectional study. BMC Pregnancy and Childbirth. 2020; 20: 1-10.

[12] Husada D, Chanthavanich P, Chotigeat U, Sunttarattiwong P, Sirivichayakul C, Pengsaa K, et al. Predictive model for bacterial late-onset neonatal sepsis in a tertiary care hospital in Thailand. BMC Infectious Diseases. 2020; 20: 1-11.

[13] Guo J, Luo Y, Wu Y, Lai W, Mu X. Clinical characteristic and pathogen spectrum of neonatal sepsis in Guangzhou city from June 2011 to June 2017. Med Sci Monit. 2019; 25: 2296-2304.

[14] Bhagat R, Hussain SQ, Gattoo IA, Wani SA. Incidence of meningitis in late onset sepsis. Int J Contemp Pediatr. 2015; 2(2): 96-102.

[15] Ismael AM, Quadri S. Incidence, Clinical Profile and Etiology of Meningitis in Term Neonates with Clinical Sepsis. Galore International Journal of Health Sciences and Research. 2019; 4(3): 51-9.

[16] Barichello T, Fagundes GD, Generoso JS, Elias SG, Simoes LR, Teixeira AL. Pathophysiology of neonatal acute bacterial meningitis. Journal of Medical Microbiology. 2013; 62: 1782-9.

[17] Macías-Parra M, Saltigeral Simental P, Weber MAR, Puente SG, Diaz-Jimenez V. Neonatal Bacterial Meningitis and Late onset sepsis in a Third Level Hospital in Mexico City during a 32 Year Period: Clinical Characteristics and Risk Factors for Mortality and Neurologic Sequelae. EC Paediatrics. 2019: 3-16.

[18] Pan T, Zhu Q, Li P, Hua J, Feng X. Late-onset neonatal sepsis in Suzhou, China. BMC Pediatrics. 2020; 20(261): 1-7.

[19] Shaha CK, Dey SK, Shabuj KH, Christi J, Mannan MA, Jashimuddin, et al. Neonatal sepsis - a review. Bangladesh J Child Health. 2012; 36(2): 82-9.

[20] Tiskumara R, Fakharee SH, Liu CQ, Nuntnarumit P, Lui KM, Hammoud M, et al. Neonatal infections in Asia. Arch Dis Child Fetal Neonatal Ed. 2009; 94: 144–8.

[21] Huang FK, Chen HL, Yang PH, Lin HC. Bird's Eye View of a Neonatologist: Clinical Approach to Emergency Neonatal Infection. Pediatrics and Neonatology. 2016; 57: 167-73.

[22] Chang CC, Sun JT, Chu FY. Bacterial sepsis, neutrophils and intracellular organisms. An International Journal of Medicine. 2017; 110(6): 393–4.