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The Risk Factors of Early Onset Neonatal Sepsis

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Abstract: *Introduction:* Neonatal sepsis is one of the major causes of morbidity and mortality in newborn. Early onset neonatal sepsis (EONS) is a severe disease and has high mortality rate. The clinical signs of EONS are nonspecific and the confirmation of diagnosis may consuming time. Therefore, the diagnostic approach is necessary by considering the risk factors. *Objective:* The aims of this study are to identify the risk factors of newborn infants whose mother has risk factors of sepsis affecting the occurrence of EONS. *Methods*: This is a cohort retrospective study, conducted from January 2013 to June 2014 in Neonatology Installation of Dr. Wahidin Sudirohusodo hospital, Makassar. The sample population included newborn infants whose mother has risk factors of sepsis. The information of the risk factors from infant and diagnoses of EONS was obtained from their medical record. Multivariate analysis and logistic regression formula were performed to predict the occurrence of EONS. There were 221 samples: 62 cases of EONS and 159 of control. *Results*: The results of multivariate analysis revealed 3 risk factors from infant which were associated to EONS: APGAR score <7 (p= 0.000, AOR 14.05 with 95% CI 5.48-35.98), gestational age <37 week (p= 0.000, AOR 13.45 with 95% CI 3.91-46.26), birth weight <1500 gram (p= 0.04, AOR 4.9 with 95% CI 1.08-22.25). *Conclusion*: Based on this study, it concluded that the risk factors of EOS were: APGAR score, gestational age and birth weight.

Keywords: Early Onset Neonatal Sepsis, Risk Factors, Infants

1. Introduction

Neonatal mortality (NM) until nowadays is still the highest mortality in human life. It has a close relation to infant mortality rate (IMR), which used as the indicator of health development in countries.[1] In 2009, WHO reported that there is 3.3 million of neonatal mortality from 6 million of infant mortality.[2] In Indonesia, infant mortality rate is 19/1000 live births or around 236/days and 10 people per hour. Sepsis becomes the biggest cause with presentation of 20.6% from age 0-28 days and around 12% of age 0-6 days.[3]

Neonatal sepsis is a clinical syndrome occurs because of microorganism invasion into the blood on the first month of life.[4] Basically, the fetuses were still wrapped by layers of amnion adequately shielded from bacterial flora's mother because of the cervical plug, which is the placenta barrier and antimicrobial proteins and peptides in it.[5, 6] Even though the probably of microorganism contamination can occurs by a several ways, such as transplacental, which is the ascending infection from cervical or by the birth canal during the birth process.[7] On exposed, the babies are shaping the immune response to maintain their body from the infection.[8] Several factors of mother, babies, and environment are contribute to the infection exposed and non optimal of NM immunologic response so as the newborn become susceptible to be infection.[9]

There is a dilemma on the sepsis management, that if there is a delay of treatment will increase the mortality rate of over 50%. If not be therapy while the over diagnosis happens, due to the non particular of clinical illustration will make the over treatment and harm the patient and his/her family. Hence, the clinic decision by the clinicians against the newborn that is apparently healthy or with a minimal of sepsis symptom. Furthermore, even asymptomatic bacteraemia can be done accuracy and faster with a risk factor consideration considering of several support examine to confirm the diagnosis need a lot of time.[10] This study aims to identification the risk factors of neonatal from the mother with risk factor of EONS occurrence.

2. Materials and Methods

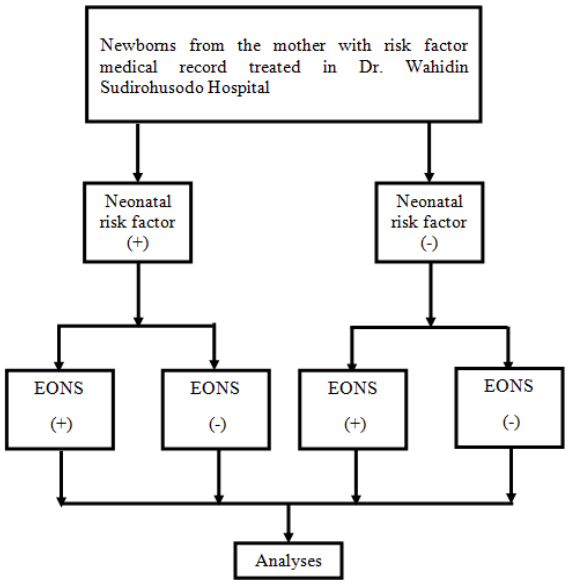

Figure 1. *Study flow scheme*

An observational with a retrospective cohort study conducted at neonatology installation of Dr. Wahidin Sudirohusodo Hospital in Makassar, from January 2013 to June 2014. We assess the incidence and identification of the neonatal risk factors relation to the EONS by using a data from patient's medical records. Newborn, aged under or of 3 days birth consecutively recruited. Written informed consent was obtained from the patients' parents or legal guardian following full and detail explanation regarding the study's protocol.

Study samples are from all the affordable population that met the inclusion and exclusion criteria. The inclusion criteria are all the newborn from the mother with risk factor treated in Dr. Wahidin Sudirohusodo and age under or of 3 days. While, the exclusion criteria are the newborn with congenital abnormalities, birth from the mother with TORCH and the patient with incomplete data. The ways of taking sample is from the patient medical records related to the study. Then it is grouped into two group of neonatal with early onset neonatal sepsis (EONS) and non EONS, and done recording of infant infection risk factors.

All the data obtained are noted in the study data form, then grouped based on the objectives and types of data. Then, the data is analyzed to assess the relationship of the infection risk factor of the infant with EONS by the suitable statistical methods includes the univariate, bivariate, and multivariate analysis.

3. Results

3.1. Sample Characteristics

Table 1 shows the characteristics of study sample. Total of the study samples are 221, with 99 (44.8%) male and 122 (55.2%) female. There are 25 samples (11.3%) with the maternal fever and 196 samples (88.7%) with the non maternal fever. Samples of mother with leukocytosis are 129 (58.4%), while the non leukocytosis is 92 (41.6%). The mother samples of premature rupture of membrane (PROM) are 96 (31.2%) and the non PROM are 125 (56.6%). There are 32 samples (14.5%) with the meconium stained amniotic fluid (MSAF), while the other of 189 samples (85.5%) are not. The mean of gestational age and birth weight respectively are 37 weeks and 2596 grams.

Table 1. *Sample characteristics study.*

No.	Sample characteristics	Total (n = 221) (%)
1.	Sex	
	Male (%)	99 (44.8)
	Female (%)	122 (55.2)
2.	Mother temperature	
	Maternal fever ≥38ºC (%)	25 (11.3)
	Non maternal fever <38ºC (%)	196 (88.7)
3.	Mother leucocytes	
	Leukocytosis ≥18000(%)	129 (58.4)
	Normal <18000(%)	92 (41.6)
4.	PROM	
	PROM (%)	96 (43.4)
	Non PROM (%)	125 (56.6)
5.	Amniotic color	
	Meconium (%)	32 (14.5)
	Normal (%)	189 (85.5)
6.	Apgar score	
	<7 (%)	69 (31.2)
	≥7 (%)	152 (68.8)
7.	Gestation (weeks)	
	Range	24 – 43
	Average (DS)	37.06 (3.44)
8.	Birth weight (gram)	
	Range	780 – 4490
	Average (DS)	2596.81 (808.71)

M: Male, F: Female ( ): Presentation value

3.2. An EONS Risk Factors Prognostic

Table 2 shows the relationships of the EONS occurrence with the several infants risk factor. Statistical analysis show there is no significant difference based on sex, with value p= 0.203 (p>0.05). Statistical test result shows a significant difference of the EONS occurrence in infants with Apgar score <7 compared to ≥7 with value p= 0.000 (p<0.001). Crude odds ratio (COR) value = 11.57 with 95% CI (5.84-22.948). The EONS occurrence is also has a significance difference between the infants to the gestation of <37 and ≥37 with p= 0.000 (p<0.001). Crude odds ratio (COR) value = 28.25 with 95% CI (12.54-63.61). Statistic test result is also shows a significance difference between the birth weight <1500 gram compared to ≥1500 gram with value p=0.000. It is stated with COR value = 28.875 with 95% CI (10.4-80.11).

Table 2. *Results of bivariate analysis EONS incidence relationship with risk factors from newborns*

Variable	Outcomes		Value p	*COR*	95% CI
	EONS	Non EONS			
Sex					
Male	32 (51.6%)	67 (42.1%)	0.203	-	-
Female	30 (48.4%)	92 (57.9%)			
Apgar score					
<7	43 (69.4%)	26 (16.4%)	0.000	11.577	5.840 – 22.948
≥7	19 (30.6%)	133 (83.6%)			
Gestation					
<37 weeks	42 (67.7%)	11 (6.9%)	0.000	28.255	12.549-63.616
≥37 weeks	20 (32.3%)	148 (93.1%)			
Birth weight					
<2500 gram	45 (72.6%)	27 (17.0%)	0.000	12.941	6.46-25.92
≥2500 gram	17 (27.4%)	132 (83.0%)			
Birth weight					
<1500 gram	30 (48.4%)	5 (3.1%)	0.000	28.875	10.4–80.11
≥1500 gram	32 (51.6%)	154 (96.9%)			

3.3. Identification of the EONS Risk Factors

Table 3 shows the analysis results of double logistic regression risk factors to the EONS occurrence. Multivariate analysis result for the Apgar score obtained the AOR 14.05 with 95% CI (5.45-35.98) which means the infants with Apgar score <7 in the first minute has a 14.05 times greatest of EONS occurrence compared to ≥7. On gestation, AOR 13.45 with 95% CI (3.91-46.26) which means the gestation <37 weeks has a 13.45 times greatest of the EONS occurrence compared to the gestation ≥37 weeks. While for the birth weight, AOR 4.9 with 95% CI (1.08-22.25) which means the infants with birth weight <1500 gram has a risk of 4.9 times greatest of EONS occurrence compared to ≥1500 gram. Moreover, the birth weight <2500 gram into the multivariate analyses is not the risk factor with value p= 0.16 (p>0.05).

Table 3. *Results of double logistic regression risk factors to the EONS occurrence.*

No.	Variable	B	E.S	Df	*p*	AOR	95% CI
1.	Apgar score (AS)	2.643	0.48	1	0.00	14.05	5.487-35.98
2.	Gestation (G)	2.599	0.63	1	0.00	13.45	3.91-46.26
3.	Birth weight (BW) <1500 gram	1.589	0.77	1	0.04	4.9	1.08-22.25
4.	Constanta (a)	-3.156	0.41	1	-	-	-

B: Regression coefficient E.S : Error standard

4. Discussion

This study obtained the EONS incidence as 28% from 221 of newborns from the mother with risk factor. This incidence is not different with the reported by *Canadian Pediatrics Society*, which the EONS occurrence prevalence by the mother with infection risk factor about 20%.[11] Chacko and Sohi are also report the EONS incidence is 20.6% in newborn from the mother infection risk factor, while the mother without risk factor is only 0.5%.[12]

Sexual dimorphism from the human immune response is quite clear; female produces the more active of cellular immune reaction and humoral so that they are more resistant to the infection.[13] But, our result shows there is no relationships between the sex to the EONS (p= 0.203). This is accordance with the report by Shah et al., with p= 0.2.[9] The study in India also reported that there is no significant between both of the sex with infection rate between male (2.05%) and female (2.08%).[12]

We also found that the Apgar score <7 in the first minute have a risk of 14.05 times (95% CI 5.487-35.987) to the EONS occurrence. Chacko and Sohi also reported the EONS occurrence on infants with Apgar score <7 in the first minute increased 11.1 times significant with p= 0.001.[12] Apgar score <7 in the first minute is also reported by Shah et al., have a significant with each OR is 5.7 to the EONS occurrence.[9] Even the research in America reported the EONS risk increased to 36.25 times if reach to fifth minute of Apgar score <6.[14] In general, the Apgar score at the first minute associated with the Hydrogen Potential (pH) cord blood and intrapartum depression and not associate with the outcomes, whereas the Apgar score then reflects the infants changes condition on the resuscitation performed.[15] Perinatal hypoxia-ischemia can caused by several factors, but with the consistent result from the above study shows that the infant infection factor from the perinatal is one of the main factor causes of low Apgar score in the first minute.[16]

Our study result shows that the gestation is also the risk factor with 13.45 times (95% CI 3.91-46.26). In Inggris, the infants birth <37 weeks have a risk 12.1 times (95% CI 2.7 to 53.8) obtained EONS because of GBS (group B streptococcus) compared to the term baby.[17] The same case also reported from Nepal, with a risk 4.85 times EONS happens on the preterm baby.[9] In Mexico reported the preterm baby have a risk of 2.19 times on EONS while on LONS (late onset neonatal sepsis) is not significant.[18] This is

happens because of the preterm baby have a limited capacity in increasing the neutrophils production in order to response the infection and the neutrophils dysfunction.[19] The impaired neutrophil function have reported apparent when it is <30 weeks of gestation.[20] Rebuck et al., found the L-Selectin expression on newborn with >32 weeks of gestation is about 40% of adult.[21] This amount is equal to the term infants. Carr et al., also reported the newborn <32 weeks have a low sFcRIII concentration and increase faster when it is 33-36 weeks of gestation.[22] sFcRIII is responsible for initiating opsonization and phagocytosis.The decreased of opsonization and complement protein deficiency also occurs whereas both of it are the main component of the non specific immunity which is the first line of defense against microorganisms in neonates. It makes the newborn is susceptible to infection and often develop into a severe infection.[19] Besides, IgG transfers begin since 12 weeks of gestation and reach out the 400 mg/dl in 32 weeks of gestation.[23]

Bhat and Baby reported the low birth weight have a risk of EONS 10 times compared to the normal birth weight.[24] Whereas according to Shah et al., the low birth weights (LBW) have a significant with Odds Ratio 4.85.[9] But, Leal et al., shows LBW (≤2500 g) is not a risk factor neither to the EONS or LONS.[18] In our study, low birth weight did not have a significant to the EONS occurrence (p= 0.162). This is occurs because of the LBW on our samples are dominated by the birth weight 1900-2499 gram which a birth weight of the late preterm baby while the low immunity in the LBW mainly occur on the gestation <32 weeks or among the birth weight <1500 gram. It is strength by the research by Wolkowiez et al., reported there is no significant between the term baby to the late preterm with a lowest birth weight of 1920 gram to EONS (p= 0.126).[25] Therefore, we analyzed again the logistic regression with the birth weight category <1500 gram (very low birth weight (VLBW)) and ≥1500 gram. We found that the VLBW are more common in a risk of 4.9 times (95% CI 1.08-22.25) to the EONS occurrence. In America, the EONS incidences have increases to 10 times higher than the VLBW.[26] Benitz et al., found that the EONS risk is increase along with a decrease in the birth weight.[27] Physical barriers such as skin, the mucosa membrane and chemicals that are antibacterial or inhibit the adhesion of bacteria to the host began mature around 32-34 weeks of gestation and accelerated after the birth. That's why the IgA level is produces by the mucosa protection layer, lowest on the VLBW.[23] Seidel et al., found the same levels of sIgA between newborn with 30 weeks of gestation (range of birth weight 1200 grams) with the term baby.[28] VLBW also have the ability to decline significantly in the case of actin filament formation and neutrophils plasticity of the transmigration.[23] Gahr et al., reported the interference in respiratory burst on newborn <2000 gram.[29] VLBW also only had a terminal cytotoxic components value such as C3 and C3b about 10% or less of the content of his mother and difficulty in activating the complement through the lectin and alternative way. Consequently, the result is a complement dysfunction of VLBW, such as a chemotaxis function, opsonization and killed the pathogens through the membrane attack complement. In VLBW also occurs the deficiency of molecular reactants phase such as CRP, inhibitor protein, A amilod protein and several of the coagulation protein which have a function to increase the resistance to the infection. VLBW had a lot of neutrophil in circulatory pool but it reserves in the bone marrow is only about 20% compared to the term baby and adults so that the state of sepsis occur severe neutropenia.[23, 30]

From our study, we obtained a regression model. With the regression model like this, the clinicians can predict the EONS occurrence on the infants of the mother with risk factor; because the EONS is an acute disease with a high mortality, whereas the diagnosis approach by considered the risk factor with a regression model above can avoid the miss cases and the delay treatment.[31]

The strength of our study is using a multivariate analysis with a tight operational definition, so that the risk factor obtained is an independent factor. The other strength of this study is the risk factor analyzed can be discovering easily by the history and physical examine so the clinicians are easily to predict the EONS occurrence. Therefore, we are still using medical records and may need a further study with a prospective cohort method to obtain a stronger causal relationship and evaluate our regression model.

We concluded that the EONS occurrence frequency on newborn of the mother with risk factor is 28%. The risk factors of EONS from the infants of the mother with risk factor are Apgar score <7 (AOR 14.05), gestation <37 weeks (AOR 13.45) and birth weight <1500 gram (AOR 4.9) while the sex is not have any relationship with the EONS occurrence. According to the three risk factor mention above, the higher possibility of EONS occurrence is 97.53%. We suggest to do some multicenter investigation include a large sample with a better method to assess the infants risk factor relationship to the EONS.

References

[1] Aminullah A. Sepsis pada bayi baru lahir. Dalam Buku Ajar Neonatologi. Edisi I. IDAI Jakarta. 2008; 170-187.

[2] WHO. Media Centre: Newborns, reducing mortality. 2009.

[3] Departemen Kesehatan Republik Indonesia. Survei Demografi dan Kesehatan Indonesia. 2011

[4] Gomella TL, Cunningham MD, Eyal FG, Zenk KE. (ed.). Infectious Diseases. Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs. 5th Edition. McGraw-Hill Companies. 2009; 434-81.

[5] Levy O. Innate imunity of the newborn: Basic mechanisms and clinical correlates. Nat Rev Immunol. 2007;7(5): 379-90

[6] Rohsiswatmo R. Multidrug resistance in a neonatal unit and therapeutic implications. Paediatrica Indonesiana. 2006; 46: 25-31.

[7] Anderson-Berry AL, Rosenkrantz T. (2010). Neonatal Sepsis (Online). www.medscape.com.

[8] Van Der Zwet WC, Catsburg A, Van Elburg RM, Savelkoul PHM, Vandenbroucke-Grauls CMJE. Mannose-Binding Lectin (MBL) genotype in relation to risk of nosocomial infection in pre-term neonates in the neonatal intensive care unit. Clin Microbiol Infect. 2008;14: 130-135

[9] Shah GS, Budhathoki S, Das BK, Mandal RN. Risk factors in early neonatal sepsis. Kathmandu University Medical Journal. 2006; 4(2): 187-91.

[10] Chiesa C, Panero A, Osborn JF, Simonetty AF, Pacifico L. Diagnosis of neonatal sepsis: A clinical and laboratory challenge. Clinical Chemistry. 2004;50(2): 279-287

[11] Canadian Paediatric Society. Management of infant at increased risk for sepsis. Paediatr Child Health. 2007;12: 893-898

[12] Chacko B, Sohi I. Early onset neonatal sepsis. Indian Pediatr. 2005;72: 23-26

[13] Bouman A, Schipper M, Heineman M, Faas M. Gender difference in the non-specific and specific immune response in humans. American Journal of Reproductive Immunology. 2004;5(2): 19-26

[14] Soman M, Green B, Daling J. Risks factors for early neonatal sepsis. Am J Epidemiol. 1985;121: 712-19.

[15] Ringer S. Resuscitation in the delivery room. In: Manual of Neonatal Care.Ed. Cloherty J., Eichenwald E., and Stark A. 6th Ed. Wolters Kluwer. Philadelphia. 2004; 518-520

[16] Adcock L, Papile L. Perinatal Asphyxia. In: Manual of Neonatal Care. Ed. Cloherty, J, Eichenwald,E. and Stark,A. 6th Ed. Wolters Kluwer. Philadelphia. 2004: 518-520

[17] Oddie S, Emblrton N. Risk factors for early onset neonatal group b streptococcal sepsis; Case Control Study. BMJ. 2002;325(7359): 308–311

[18] Leal AY, Alvarez-Nemegyei J, Velazquez JR, Rosado-Quiab U, Diego-Rodriguez N, Paz-Baeza E, Davilla-Velazquez J. Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. BMC Pregnancy and Childbirth. 2012;12: 48

[19] Petrova A, Mehta R. Dysfunction of innate immunity and associated pathology in neonates. Indian Pediatr. 2007;74: 185-91

[20] Bhat R, Baby LP. Early onset of neonatal sepsis: Analysis of the risk factors and the bacterial isolates by using the bact alert system. Journal of Clinical and Diagnostic Research. 2011;5(7): 1385-1388

[21] Cohen-Wolkowiez M, Moran C, Benjamin DK, Cotten MC, Clark RH, Benjamin Jr DK, Smith PB. Early and late onset sepsis in late preterm infants. Pediatric Infect Dis J. 2009;28(12): 1052-56

[22] Puopolo KM. Epidemiology of Neonatal Early-onset Sepsis. NeoReview. 2008; 9(12): 571-579.

[23] Benitz WE, Gould JB, Druzin ML. Risk Factors for Early Onset Group B-Streptococcal Sepsis: Estimation of Odds Ratios by Critical Literature Review. Pediatrics. 1999;103: c77

[24] Haque KN. Neonatal Sepsis in the Very Low Birth Weight Preterm Infants: Part 1: Review of Patho-physiology. Journal of Medical science. 2010;3(1): 1-10

[25] Seidel BM, Schulze B, Schubert S, Borte M. Oral mucosal immunocompetence in preterm infants in the first 9 months of life. Eur J Pediatr. 2000;159: 789

[26] Nussbaum C. Neurophil and endothelial adhesive function during human fetal ontogeny. J. Leukor. Biol. 2012;93: 175-184

[27] Rebuck N, Gibson A, Finn A. Neutrophil adhesion molecules in term and premature infants; normal or enhanced leucocyte integrins but defctive L-Selectin expression and shedding. Clinical and Experimental Immunology. 1995;101: 183-9

[28] Carr R, Huizinga TW, Kleijer M, Davies JM. Changes in plasma FcRIII demonstrate increasing receptor production during late pregnancy and preterm birth. Pediatr Res. 1992;32: 505-8

[29] Gahr M, Blanke R, Speer CP. Polymorph nuclear leukocyte function in term and preterm newborn infants. Biology of the Neonate. 1985;48: 15-20

[30] Mussi-Pinhata MM, Rego MA. Immunological peculiarities of extremely preterm infants: A challenge for the prevention of nosocomial sepsis. J.Pediatr (Rio J.). (2005); 81: S59-S68.

[31] Gerdes JS. Diagnosis and management of bacterial infections in the neonates. Pediat Clin Neonatal Am. 2004; 51: 939-959.