

Association between neutropenia and death rate of bacterial neonatal sepsis

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Abstract

Background Neonatal sepsis remains a crucial problem with high morbidity and mortality. Not less than four million neonates die every year, 99% of which occur in developing countries with infection as the main cause (36%) of death. The prognostic factors of bacterial neonatal sepsis vary. However the death rate in neonatal sepsis with neutropenia is suspected to be higher than that in non-neutropenic condition.

Objectives The purpose of this study was to identify whether neutropenia would increase the death risk of bacterial neonatal sepsis.

Methods We conducted a retrospective cohort study. Subjects were neonates at *Instalasi Maternal Perinatal* (IMP) of Dr. Sardjito Hospital in Yogyakarta who met the eligibility criteria. During the five-year period (January 2002 – January 2007), out of 1821 cases of suspected neonatal sepsis, 365 (16.7%) were found to have bacterial cause in the culture of body's fluid (blood, urine, and cerebrospinal). Out of these 16.7% patients suffering from neutropenia, 39.6% patients died, whereas 9.1% patients were survive [RR 4.72, (95% CI: 2.49 to 8.93), $P < 0.01$].

Conclusion Neonates suffering bacterial sepsis with neutropenia had death risk 4.7 times higher than those who did not have neutropenia. [Paediatr Indones 2008;48:284-7].

Keywords: bacterial neonatal sepsis, neutropenia, death rate

Neonatal sepsis is a clinical syndrome characterized by systemic symptoms and bacteremia occurring in the first month of life.¹⁻³ Generally, infection in the first month of life is associated with high death rate, i.e., 13 to 15%.⁴ The incidence of sepsis in neonates is 1 to 8 per 1000 live births and increases to 13 to 37 per live births in infant less than 1500 grams.¹

Every year, four million neonates die, 99% of which occur in developing countries with low Gross National Product, particularly in the Central & South Asia.⁵ Indonesia is one out of ten countries which have very high neonatal death rate.⁵ The neonatal mortality rate in 12 hospitals in Indonesia according to a survey conducted by *Unit Koordinasi Kerja Perinatologi* (Neonatology Work Coordinating Unit) of Indonesian Pediatric Society in 2003 was 75.2 per 1000 live births, 28.4% of which were caused by infection.⁶

Considering the neonatal sepsis problems complexity, special treatment is always needed, which

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in turn, requires high cost of treatment. Management of neonatal sepsis remains a problem recently due to difficulty establishing the diagnosis.^{7,8}

The prognosis of neonatal sepsis depends on many factors, including the presence of complications and several laboratory characteristics. One of these is neutropenia; neutropenia that persists along with emptying neutrophils stored in bone marrow is associated with poor prognosis.⁹⁻¹¹ We aimed to find out how high the prevalence of neutropenia in bacterial-neonatal sepsis at Dr. Sardjito Hospital, Yogyakarta, and whether neutropenia was associated with increased death rate.

Methods

We conducted a retrospective cohort study to investigate the association between neutropenia and outcome of bacterial-neonatal sepsis. Data were taken from the medical records of *Instalasi Maternal Perinatal* (IMP) Dr. Sardjito Hospital Yogyakarta. We excluded neonates with alloimmune neutropenia, inherited disorders, or those with incomplete records.

With degree of significance 0.05 and 80% power to detect a relative risk of 3, the total minimum number of subjects needed for the study was 40. The independent variable in this study was neutropenia, whereas the dependent variable was death and survival rate. This study included neonates suffering from neonatal sepsis (positive culture of body fluid) from January 2002 to January 2007. Data were analyzed using SPSS.

Results

During the period of January 2002-January 2007 1821 cases of neonatal sepsis were identified, 365 (20%) of which were caused by bacteria in the body fluid culture (blood, urine, cerebrospinal fluid, or pharyngeal swab). The characteristics of the subjects are shown in **Table 1**. *Staphylococcus epidermidis* was the predominant cause, i.e., 106 cases (29%), and *Klebsiella pneumonia* was the leading bacteria to cause death in 35 cases (38.5%), as shown in **Table 2**.

The bivariate analyses (**Table 3**) show that neutropenia, thrombocytopenia, and anemia

Table 1. Subjects' characteristics

Variable	Number	Percentage	P
Gender			
Male	227	62.3%	0.27
Female	138	37.8%	
Gestational Age (Weeks)			
< 37	105	28.8%	0.09
37 – 42	260	71.2%	
> 42	0	0	
Sepsis onset			
Early onset	215	58.9%	0.28
Late onset	150	41.1%	
Birth weight (Grams)			
1000 – 1499	52	14.3%	0.15
1500 – 2499	137	37.5%	
2500 – 4000	176	48.2%	
> 4000	0	0	
Premature rupture of membrane			
Yes	58	15.9%	0.24
No	307	84.1%	
Fever /UTI mothers			
Yes	59	16.1%	0.13
No	306	83.3%	
Neutrophil			
Neutropenia	61	16.7%	<0.01
No neutropenia	304	83.3%	
Thrombocyte			
Thrombocytopenia	107	29.3%	<0.01
No Thrombocytopenia	258	70.7%	
Hemoglobin			
Anemia	72	19.7%	<0.01
No anemia	293	80.3%	
Referral case			
Yes	317	86.8%	0.99
No	48	13.2%	

Table 2. Characteristics of types of bacteria causing neonatal sepsis

Bacterial Agent	Died (n = 91) n (%)	Survived (n = 274) n (%)
<i>Klebsiella pneumonia</i>	35 (38.5)	60 (21.9)
<i>Pseudomonas sp</i>	18 (19.8)	25 (9.1)
<i>Serratia mercescen</i>	2 (2.2)	4 (1.5)
<i>Staphylococcus epidermidis</i>	15 (16.5)	91 (33.1)
<i>Streptococcus viridans</i>	0 (0)	6 (2.2)
<i>E. coli</i>	3 (3.3)	12 (4.4)
<i>Acinetobacter</i>	3 (3.2)	4 (1.5)
<i>Citrobacter</i>	0 (0)	3 (1.1)
<i>Enterobacter</i>	4 (4.4)	6 (2.2)
<i>Klebsiela, pseudomonas,</i> <i>Staphylococcus aureus</i>	11 (12.1)	63 (23)

Table 3. Bivariate analysis factors predicting death of bacterial neonatal sepsis

Variable	Died n (%)	Alive n(%)	RR	95% CI	P
Gender					
Male	61 (67)	166 (60.6)	1.11	(0.93 to 1.31)	0.27
Female	30 (33)	108 (39.4)	0.84	(0.60 to 1.26)	
Gestational age (weeks)					
< 37	25 (27.5)	80 (29.2)	0.94	(0.64 to 1.38)	0.09
> 37	66 (72.5)	194 (70.8)	1.02	(0.88 to 1.18)	
Sepsis onset					
Early onset	58 (63.7)	157 (57.3)	1.11	(0.92 to 1.34)	0.28
Late onset	33 (36.3)	117 (42.7)	0.85	(0.63 to 1.15)	
Birth weight (grams)					
< 2500	52 (58.4)	137 (49.6)	0.85	(0.68 to 1.05)	0.15
> 2500	37 (41.6)	139 (50.4)	1.21	(0.92 to 1.59)	
Premature rupture of membrane					
Yes	18 (19.8)	40 (14.6)	1.35	(0.82 to 2.24)	0.24
No	73 (80.2)	234 (85.4)	0.94	(0.84 to 1.05)	
Fever / UTI mothers					
Yes	19 (20.9)	39 (14.2)	1.47	(0.89 to 2.41)	0.13
No	72 (79.1)	235 (85.8)	0.92	(0.82 to 1.04)	
Neutrophil					
Neutropenia	36 (39.6)	25 (9.1)	4.34	(2.76 to 6.81)	<0.01
No neutropenia	55 (60.4)	249 (90.9)	0.66	(0.56 to 0.79)	
Thrombocyte					
Thrombocytopenia	53 (58.2)	54 (19.7)	2.95	(2.19 to 3.97)	<0.01
No thrombocytopenia	38 (41.8)	220 (80.3)	0.52	(0.41 to 0.67)	
Hemoglobin					
Anemia	30 (33)	42 (15.3)	2.15	(1.44 to 3.22)	<0.01
No anemia	61 (67)	232 (84.7)	0.79	(0.68 to 0.92)	
Referrals					
With	79 (86.8)	238 (86.9)	0.99	(0.91 to 1.09)	0.99
Without	12 (13.2)	36 (13.1)	1	(0.55 to 1.84)	

Table 4. Multivariate analysis factors of death predictors

Predictor factor	Died n (%)	Cured n(%)	RR	95% CI	P
Neutropenia	36 (59)	25 (41)	4.72	(2.49; 8.93)	<0.01
Thrombocytopenia	53 (49.5)	54 (50.5)	3.62	(2.06; 6.33)	<0.01
Anemia	30 (41.7)	42 (58.3)	2.04	(1.09; 3.81)	0.03

significantly increased the death of neonatal sepsis. Out of 61 patients with neutropenia, 36 died, 25 cases survived, while out of 304 patients with normal neutrophil count, 55 died. The relative risk (RR) of dying was 4.34 (95% CI 2.76 to 6.81; P <0.01). Anemia was found in 72 patients; 30 of which died. Out of 293 neonates without anemia, 61 died, leading to RR of 2.15 (95% CI 1.44 to 3.22; P <0.01). Multivariate analysis showed that neutropenia was the biggest risk factor causing death in bacterial-neonatal sepsis with RR 4.72 (95% CI

2.49 to 8.93; P < 0.01), thrombocytopenia with RR 3.62 (95% CI 2.06 to 6.33; P <0.01), and anemia with RR 2.04 (95% CI 1.09 to 3.81; P <0.05). See **Tables 3 and 4.**

Discussion

In this five-year study, we found 365 (20%) out of 1821 cases of neonatal sepsis were caused by bacteria; out of the 365 cases, neutropenia in those cases (of bacterial

neonatal sepsis of this study) was found in 16.7%. This figure was smaller than that studied by Funke *et al*,¹⁰ in which the frequency of neutropenia was 32.8%. Gender, prematurity, birth weight, maternal infection or referrals were not predictors of death of bacterial neonatal sepsis. These results were similar to a study by Schiber *et al*.⁸

Normal functions of neutrophils include chemotaxis or mobility and migration of phagocytic cells into the bacteria or inflammation.^{10,12} The ability to transform or deformability of neutrophil membrane in neonates is insufficient, so that it may increase the rigidity of membrane which eventually causes lack of ability to do chemotaxis. Neutropenia could happen because of the imbalance between production and destruction of neutrophil.

Both bivariate and multivariate analyses showed that neutropenia, thrombocytopenia, and anemia were significant risk factors which could increase death rate in neonatal sepsis. This was similar to previously-mentioned study by Funke *et al*,¹⁰ which had increased mortality rate in the group with neutropenia by 23% compared to the group without neutropenia. Neonatal sepsis with low birth weight and prematurity with neutropenia had higher mortality rate compared to that without neutropenia.

Other study by Weber *et al*⁹ on the death risk factor in neonatal sepsis using outcome of clinical parameter (respiratory difficulty, dehydration, hypotension, extending capillary perfusion, tachycardia, oliguria, edema, abdominal distension, diarrhea, fever), laboratory (leukocytosis, leukopenia, thrombocytopenia, number of stem cells, results of urine, faeces, and cerebrospinal fluid cultures) showed that neonatal sepsis along with leukopenia caused death by 29.4% compared to that without leukopenia. Significant thrombocytopenia increased death on neonatal sepsis with $P = 0.01$, respiratory difficulty $P < 0.001$ and extending capillary perfusion network also caused increased death risk $P < 0.05$. Anemia was not included as the risk factors.

In conclusion, neonates with bacterial sepsis and neutropenia have 4.7 times risk to die compared to those without neutropenia. In such patients, thrombocytopenia served as the death risk predictor

and contributed 3.6 times compared to those without it, whereas anemia could cause the death risk two times higher than that without it.

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