Original Article

Incidence and factors associated with mortality of neonatal sepsis

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Abstract

Background Neonatal sepsis is one of the major causes of mortality and long term morbidity in neonates, particularly in premature and low birth weight infants. The incidence of neonatal sepsis varies from 1 to 4 in 1000 live births in developed countries and 10 to 50 in 1000 live births in developing countries. The mortality rate of neonatal sepsis remains high, especially in developing countries.

Objective To describe the incidence, mortality rate, and factors associated with mortality in neonatal sepsis in Sanglah Hospital, Denpasar.

Methods A retrospective, cohort study was conducted in the Perinatology Ward, Department of Child Health, Sanglah Hospital, Denpasar, Bali from January to December 2008. One hundred thirty-eight patients with neonatal sepsis were enrolled in this study. Patients' characteristic data were collected including sex, mode of delivery (spontaneous, non-spontaneous), condition at birth (vigorous, asphyxic), gestational age (premature, full term), birth weight (<2500 grams, >2500 grams), and sepsis classification (early onset sepsis, late onset sepsis). Outcomes were grouped into alive and dead.

Results A total of 138 cases of neonatal sepsis were reviewed, 59.4% of whom were boys, 63.0% spontaneously delivered, 39.1% asphyxic, 53.6% with low birth weight, 50.7% premature, and 84.8% with early onset sepsis. The incidence of neonatal sepsis was 5% of babies admitted, with a mortality rate of 28.3%. Low birth weight and prematurity were significantly associated with mortality in neonatal sepsis (RR 8.4, 95% CI 2.4 to 29.0, P = 0.001 and RR 3.4, 95% CI 1.0 to 11.0, P = 0.042, respectively).

Conclusion The incidence of neonatal sepsis in Sanglah Hospital was 5% of babies admitted, with a mortality rate of 28.3%. Low birth weight and prematurity were significantly associated with mortality in neonatal sepsis. [**Paediatr Indones. 2011;51:144-8**].

Keywords: neonatal sepsis, mortality, risk factors

The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all deaths in under-five year olds) are due to neonatal sepsis and that 42% of these deaths occur in the first week of life. Globally, the main direct causes of neonatal mortality are thought to be preterm birth (28%), severe infections (26%), and asphyxia (23%).[1] The incidence of neonatal sepsis varies from 1-4/1000 live births in developed countries to 10-50/1000 live births in developing countries. The susceptibility of a neonate to sepsis is multifactorial, and can be related to immaturity of humoral, phagocytic and cellular immunity (usually appearing in preterm and low birth weight infants), hypoxia, acidosis, and metabolic derangements.[2,3] The incidence of neonatal sepsis is also influenced by economic status, mode of delivery, race, sex (males are 4 times more affected than females), and standard of neonatal care received, and incidence also varies from nursery to nursery depending on conditions predisposing infants to infection.[4-6]

In developing countries, neonatal mortality resulting from all causes of neonatal sepsis is about

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34 per 1000 live births, occurring mainly in the first week of life. In developed countries, it is 5 per 1000 live births.[7] In Malaysia, the incidence of neonatal sepsis was 5-10% and mortality rate was 23-50%. In RSCM, Jakarta, from January-September 2005 the incidence of neonatal sepsis was considered to be 13.68% of all live births with a mortality rate of 14.18%.[8] In Sanglah Hospital, a previous study from January 2003-December 2004 reported the incidence of neonatal sepsis to be 5.3% with a mortality rate of 56%.[9]

The aim of our study was to find the incidence of neonatal sepsis and to identify factors (sex, mode of delivery, asphyxia, gestational age, birth weight, and time of onset of sepsis) associated with mortality from neonatal sepsis in Sanglah Hospital. It is hoped that preventive strategies may be instituted to decrease morbidity and mortality from neonatal sepsis.

Methods

We performed a retrospective, cohort study in the Perinatology Ward at Sanglah Hospital from January 1, 2008-December 31, 2008. We included all babies with neonatal sepsis. Exclusion criteria were incomplete medical records and self-discharge against medical advice. All babies born at Sanglah Hospital were recorded at birth, while referral patients were recorded on admission.

Sample size was calculated using a relative risk of 1.5, $\alpha = 5\%$, $\beta = 10\%$ and risk factor proportion of 28%. The minimum number of subjects required was 96.

Neonatal sepsis is a clinical syndrome accompanied by bacteremia occurring during the first month of life. In this study, sepsis was diagnosed based on clinical symptoms and positive blood cultures. Sepsis was classified into early onset sepsis if it occurred beginning <72 hours of life and late onset sepsis if it occurred beginning >72 hours of life. Outcomes were defined as the patient condition on discharge, and grouped into alive and dead. Possible risk factors for mortality were: mode of delivery, grouped into spontaneous or non-spontaneous delivery; condition at birth, grouped into asphyxia if the baby did not immediately cry with Apgar score <7 at 1 minute or vigorous if the baby immediately cried with Apgar score ≥ 7 at 1

minute; birth weight measured within 1 hour after birth, grouped into <2500 grams and ≥ 2500 grams; gestational age determined based on the first day of last period or New Ballard Score (NBS), and sex, grouped into boys or girls.

Characteristics of the study subjects were collected. Chi-square method was used to examine differences between groups and logistic regression method was used for multivariable analysis of the significant risk factors. A P value of <0.05 with a 95% confidence interval were considered statistically significant. This study was approved by the Ethics committee of Udayana University Medical School/ Sanglah Hospital, Denpasar, Bali.

Results

Of the 3152 neonates who were admitted at Sanglah hospital, 158 had neonatal sepsis. Twenty of these babies were excluded as 17 self-discharged against medical advice and 3 had incomplete medical records. Therefore, we included 138 babies with neonatal sepsis in this study. The incidence of neonatal sepsis was 5%.

Based on the data on patient characteristics, most mothers were between 18-35 years old (87.7%), and most reached a senior high school level of education (44.2%). Primipara was the most common gravida (52.9%), and 92.0% received antenatal care more than 3 times during pregnancy. (**Table 1**)

Table 1. Characteristics of neonatal sepsis patients

Characteristics	Dead (N=39)	Alive (N=99)	Total (N=138)	Percentage of total
Age of mother, years				
≤ 18	2	5	7	5.1
> 18-35	34	87	121	87.7
> 35	3	7	10	7.2
Education of mother				
University	3	8	11	8.0
Senior high school	18	43	61	44.2
Junior high school	9	23	32	23.2
Elementary school	9	25	34	24.6
Gravida				
1	20	53	73	52.9
2	12	30	42	30.4
≥ 3	7	16	23	16.7
Antenatal care				
≥ 3 times	36	91	127	92.0
< 3 times	3	8	11	8.0

Table 2. Risk factors of mortality in neonatal sepsis

Variable	Outcome		RR	95% CI	P
	Alive (N=99)	Dead (N=39)			
Sex:					
Boys	64	18	0.58	0.34 to 0.99	0.04
Girls	35	21			
Mode of Delivery:					
Spontaneous	64	23	0.84	0.49 to 1.44	0.53
Non Spontaneous	35	16			
Asphyxia:					
Yes	57	27	0.69	0.38 to 1.24	0.20
No	42	12			
Gestational Age:					
Premature	35	35	8.50	3.19 to 22.62	0.001
Aterm	64	4			
Birth Weight (grams):					
< 2500	40	34	5.88	2.44 to 14.13	0.001
≥ 2500	59	5			
Sepsis Classification:					
Early onset sepsis	83	34	1.22	0.54 to 2.76	0.62
Late onset sepsis	16	5			

Table 3. Multivariate logistic regression test based on birth weight and gestational age

Variable	RR	95% CI	P
Premature gestational age	3.39	1.043 to 11.035	0.042
Low birth weight	8.41	2.442 to 28.965	0.001

We found that most cases of neonatal sepsis occurred in boys (59.4%), were delivered spontaneously (63.0%), and had asphyxia (60.9%). Most patients were also born prematurely (50.7%) and weighed less than 2500 grams at birth (53.6%). Of the 138 babies with neonatal sepsis, most cases (84.8%) were early onset sepsis. The mortality rate was 28.3%. Mortality rate of neonatal sepsis significantly correlated to low birth weight and premature gestational age (both with P=0.001). **(Table 2)**

Further analysis by multivariate logistic regression test showed that gestational age and birth weight were significantly associated with mortality by neonatal sepsis. **(Table 3)**

Discussion

In developing countries, neonatal sepsis remains to be a major cause of mortality and morbidity in spite of recent advances in technology and therapeutics. Some factors influencing sepsis in newborns are immature immune system, decreased phagocytes in the white cell population, decreased cytokine production and weak humoral immunity.[10-12] Various maternal, fetal, and environmental factors also contribute to sepsis in newborns. Some maternal factors are premature rupture of membranes, maternal fever within 2 weeks prior to delivery, meconium-stained amniotic fluid (MSAF), foul smelling amniotic fluid and instrumental delivery. Fetal contributing factors include low birth weight, premature gestational age, and low Apgar score**.**[8,13]

The incidence of neonatal sepsis was 5% at Sanglah Hospital. Incidence varies from nursery to nursery and within the same nursery at different time periods. A cohort study in Israel, showed that from 15,839 infants, 2.4% had an episode of early onset sepsis.[13] Stoll's review put the global incidence of neonatal sepsis at 5-6 per 1000 live births, similar to that in South and South-East Asia, 6-21 per 1000 live births in sub-Saharan Africa, 1.8-12 per 1000 live births in the Middle East and North Africa, and 2.9 per 1000 live births in the Americas/Caribbean.[14] In Songklanagarin Hospital, a major tertiary referral institution in southern Thailand, the incidence of neonatal sepsis was 4.3%.[3] The incidence of neonatal sepsis with positive blood cultures from December 2006-July 2007 at RSCM, Jakarta was 6.4%.[15] The differences in incidence of sepsis may be due to geographical, racial, socio-economic, cultural, technological, and differing definitions in making a diagnosis of neonatal sepsis.

Mortality from neonatal sepsis in this study was 28.3%, a decline from 56% in Sanglah Hospital in 2003-2004.[9] This decrease was probably due to an improved approach in diagnosing neonatal sepsis at this hospital, including in the analysis of clinical symptoms, risk factors for sepsis (major and minor), and septic workup**.** With this approach, neonatal sepsis can be diagnosed more accurately. In addition, the neonatal intensive care unit (NICU) is well equipped and has qualified human resources. High quality laboratory diagnostics also help in the performing of septic workups. We attribute decreased sepsis mortality to the improved diagnosis and management of neonatal sepsis and Sanglah Hospital.

Mortality rate of neonatal sepsis varies between hospitals and between countries. The mortality of neonatal sepsis at Basrah Maternity and Children Hospital, Iraq was 44.2%,[4] while a lower mortality rate were reported at Sao Paulo State University

(UNESP), Brazil (18%),[17] and also at University Hospital of the West Indies, Jamaica (6.7%).[10] In Tehran, Iran, mortality was 15.1%.[18] In Indonesia, Cipto Mangunkusumo Hospital in Jakarta reported that the mortality of neonatal sepsis was 14.18%,[8] while that of Moewardi Hospital, Surakarta was 40%.[16] These differences in mortality rates in neonatal sepsis among different countries may be explained by many factors, e.g., socioeconomic, geographical and racial factors, use of ventilators, incubators, different microorganisms present and different antibiotics used.[2,4,5] In this study, most deaths occurred because infants were unable to be admitted to the NICU because of limited capacity. They were admitted to the nursery ward where equipment such as incubators and monitors were limited and mechanical ventilators were unavailable. In addition, blood culture results came late so that more targeted therapy was given late.

We have identified low birth weight and prematurity to be associated with mortality in neonates with bacterial sepsis, similar to previous studies in various countries, developing and developed. Jumah *et al*[4] found the predictive factors for an outcome of death by neonatal sepsis to be low birth weight, prematurity, thrombocytopenia, neutropenia, positive blood culture for *Klebsiella* spp, prolonged capillary refill time, sclerema and signs of dehydration. Prematurity, very low birth weight and female gender were factors also associated with poor outcomes.[10] The association of prematurity with mortality of neonatal sepsis may be due to deficiencies in humoral and cellular immunity. Transplacental maternal antibodies primarily mediate humoral immunity, hence premature infants are less likely to receive as many maternal immunoglobulins (Ig) as term infants. Premature infants have extremely low immunoglobulin levels (except for IgG) to specific maternal antigens, because such Ig is passively transferred across the placenta during the last trimester of pregnancy.[10,11,16,19] Furthermore, premature infants need prolonged hospitalization, which increases the risk of nosocomial infections.[4,10,20]

A limitation of our study was not including other variables, such as clinical signs and symptoms, use of antibiotics, and results of blood cultures which all probably affect mortality by neonatal sepsis. Due to our limited independent variable measurements, we suggest further research on factors associated with mortality by neonatal sepsis.

In conclusion, the incidence of neonatal sepsis at Sanglah Hospital was 5% of inpatient neonates, with a mortality rate of 28.3%. Low birth weight and prematurity were associated with mortality in neonatal sepsis. Strategies aimed to decrease mortality in neonates with sepsis must include measures that will decrease the incidence of prematurity and low birth weight infants.

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