Clinical and laboratory characteristics and short - outcome of neonatal sepsis

Nguyen Thi Thanh Binh[1*], Hoang Mai Linh[2#], Nguyen Cong Tien[3]

(1) Department of Pediatrics, University of Medicine and Pharmacy, Hue University

(2) Pediatric Center, Hue Central Hospital, Vietnam

(3) Tam Tri Hospital, Da Nang city, Vietnam

[#]Co-first author

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Objectives: To describe clinical features and laboratory findings and to investigate factors associated with neonatal sepsis mortality. **Subjects and methods:** A prospective cohort study was conducted involving seventy-eight patients diagnosed with neonatal sepsis with positive blood cultures at the Neonatal Intensive Care Unit, Pediatric Center, Hue Central Hospital. **Results:** The study showed that neonatal sepsis occurred most frequently in preterm infants <34 weeks gestation (51.3%) and weighing less than 1500 grams (37.2%). Late-onset sepsis was the most frequent type of sepsis (92.3%). Clinical symptoms varied in multiple organs, often manifested as systemic, and respiratory symptoms. In terms of laboratory findings, leukocytosis (>20.000/mm^3) was observed in 25.6% of the cases, leukopenia (<4.000/mm^3) in 15.4%, thrombocytopenia (platelet count <100.000/mm^3) in 43.6%, and hyperglycemia (14.1%). Gram-negative bacteria were the most common causative pathogens (82.1%), followed by Gram-positive bacteria (17.9%). *Klebsiella pneumoniae* and *Staphylococcus aureus MRSA (+)* were the most encountered bacteria, with rates of 35.9% and 14.0%, respectively. The mortality rate associated with neonatal sepsis in this study was 16.7%. Multivariate regression analysis showed that neonates requiring invasive mechanical ventilation and those with gastrointestinal bleeding had a significantly higher risk of mortality, with odds ratio (OR)=100.6 (95% confidence interval (CI): 4.3-2370.7, p=0.004) and OR=42.3 (95% CI: 1.8-982.6, p=0.02), respectively. **Conclusions:** The mortality rate of neonatal sepsis is 16.7%. Mechanical ventilation and intestinal hemorrhage were significant risk factors for mortality in neonatal sepsis.

Keywords: *Neonatal sepsis, mortality.*

1. INTRODUCTION

Sepsis, an important form of neonatal infection, is a global challenge with high morbidity and mortality. It is estimated that 1.3 to 3.9 million newborns worldwide develop sepsis each year, resulting in 400.000 to 700.000 deaths [1]. Diagnosing sepsis in newborns is often difficult because clinical signs and symptoms and biomarkers are often nonspecific [2]. The gold standard for diagnosing sepsis is isolating the pathogen, usually from peripheral blood; however, this diagnostic method often yields late results, thereby leading to limitations in treatment decisions in the neonate's early stages [3]. Therefore, to contribute to improving the treatment of neonatal sepsis, we conducted this study with the following aims: to describe clinical and laboratory characteristics, and to investigate factors associated with neonatal sepsis mortality.

2. SUBJECT AND METHODS

2.1. Subjects

Seventy-eight neonates met the selection criteria at the Neonatal Intensive Care Unit - Pediatric Center, Hue Central Hospital.

Selection criteria: The neonates were diagnosed with sepsis and had positive blood culture results according to the European Medicines Agency (EMA) 2010 criteria [4].

Exclusion criteria: Parents who did not agree to participate in the study.

2.2. Methods

2.2.1. Study design: prospective cohort study.

2.2.2. Variables and measurements: neonatal characteristics (weight, sex, gestational age, method of birth, and postpartum support); clinical features of the nervous, respiratory, cardiovascular, and gastrointestinal systems, skin; laboratory tests

Corresponding Author: Nguyen Thi Thanh Binh
Email: nttbinh.a@huemed-univ.edu.vn; nttbinh.med@hueuni.edu.vn
Received: 16/7/2024; Accepted: 20/11/2024; Published: 25/12/2024

DOI: 10.34071/jmp.2024.6.17

(blood culture, count blood cells (white blood cells, platelets), CRP, blood glucose). All clinical and laboratory criteria for neonatal sepsis were defined according to the EMA 2010 guidelines [4]. Outcomes: Survival and death rates were recorded at discharge or death, respectively.

2.2.3. Statistical analysis: descriptive statistics were presented as numbers and percentages. Univariate and multivariate logistic regression analyses were performed to identify factors that predict the risk of neonatal mortality in sepsis cases. Statistical significance was set at $P < 0.05$. Statistical software (SPSS 20.0) was used to analyze the data.

2.2.4. Ethical Statement: A study was approved by Institutional Ethics Committee for Biomedical Research of University of Medicine and Pharmacy, Hue University, Vietnam (No. H2021/113). Written informed consent was obtained from the parents of all participants.

3. RESULTS

3.1. General characteristics of study population

The ratio of male to female neonates with sepsis was 1.4:1. Early-onset sepsis accounted for 7.7% of the cases, while late-onset sepsis comprised 92.3%. Preterm neonates were predominant in the sepsis group, representing 69.2%. Among the preterm neonates, 51.3% were born before 34 weeks of gestation. The average gestational age in the sepsis group was 33.5 ± 4.0 weeks. Most neonates in the sepsis group had a low birth weight, with 37.2% weighing less than 1500 grams. The median birth weight of the study group was 1900 grams (interquartile range: 1300-2800 grams). Cesarean section delivery occurred in 48.7% of cases. After birth, 56.4% of the newborns required postpartum resuscitation. Among these interventions, oxygen supplementation was the most frequent (23.1%). Notably, 2.6% of patients required cardiopulmonary resuscitation.

3.2. Clinical characteristics of neonatal sepsis

Table 1. Clinical characteristics of neonatal sepsis (n=78)

Sign/symptoms		Number (n)	Percent (%)
Body temperature	Hypothermia (<36°C)	4	5.2
	Fever (>38.5°C)	26	33.3
Skin	Scleroderma	5	6.4
	Jaundice	50	64.1
	Pale/white	26	33.3
	Petechiae	10	12.8
	Cyanosis	6	7.7
Cardiovascular	Heart rate> 160 bpm	36	46.2
	Heart rate ≤100 bpm	3	3.8
	Refill >3 s	15	19.2
	Sepsis shock	13	16.7
Respiratory support	Spontaneous breathing without supplemental oxygen	20	25.6
	OXyaen	35	44.9
	Continuous positive airway pressure (CPAP)	10	12.8
	Mechanical ventilation	13	16.7
Respiratory signs in spontanously breathing neonates (n=65)	Tachypnea >60 breath/minutes	35	53.8
	Bradypnea <30 breath/minutes	0	0.0
	Apnea	4	6.2
	Grunting	3	4.6
	Labored breathing	37	56.9

Gastrointestinal system	Poor feeding	22	28.2
	Vomiting	18	23.1
	Diarrhea	6	7.7
	Gastrointestinal bleeding	14	17.9
	Abdominal distension	45	57.7
	Enlarged liver	5	6.4
	Enlarged spleen	2	2.6
Neurological system	Lethargy	47	60.3
	Iritable	5	6.4
	Coma	5	6.4
	Bulging fontanelle	5	6.4
	Seizure	2	2.6
	Hypotonia	9	11.5
	Hypertonia	5	6.4

The most common manifestations were respiratory distress, jaundice (64.1%), abdominal distention (57.7%), and lethargy (60.3%), and fever (33.3%). Among neonates with sepsis, 16.7% required mechanical ventilation support. In those who did not require mechanical ventilation, tachypnea (53.8%) and labored breathing (56.9%) were the common findings. Septic shock was observed in 16.7% of neonates (Table 1).

3.3. Laboratory characteristics of neonatal sepsis

Table 2. Laboratory characteristics of neonatal sepsis (n=78)

	Variables	Number (n)	Percent (%)
White blood cells	<4000/mm^3	12	15.4
	>20000/mm^3	20	25.6
Platelet	<100000/mm^3	33	42.3
	>100000/mm^3	45	57.7
CRP	<15 mg/L	43	55.1
	≥15 mg/L	35	44.9
Glucose level	<2.5 mmol/L	6	7.7
	2.5-10.0 mmol/l	61	78.2
	>10.0 mmol/L	11	14.1
Blood culture			
Gram – negative bacteria (n=64, 82.1%)	*Klebsiella pneumoniae*	19	24.4
	Enterobacter aerogenes	10	12.8
	Klebsiella pneumoniae ESBL (+)	9	11.5
	Serratia marcescens	7	9.0
	Acinetobacter baumannii	5	6.4
	Escherichia coli	5	6.4
	Pseudomonas aeruginosa	4	5.1
	Enterobacter cloacae	2	2.6
	Escherichia coli ESBL (+)	1	1.3
	Klebsiella oxytoca	1	1.3
	Elizabethkingia meningoseptica	1	1.3

Gram-positive bacteria	*Staphylococcus aureus MRSA (+)*	11	14.0
	Staphylococcus aureus	2	2.6
(n=14, 17.9%)	*Streptococcus agalactiae*	1	1.3

Laboratory abnormalities in neonatal sepsis were high: 41.0% of neonates had leukocytosis and leukopenia, 43.6% had thrombocytopenia <100000/mm^3, CRP ≥15mg/dl was present in 44.9%, and hyperglycemia >10.0 mmol/L (14.1%) was observed. Gram-negative bacteria were the predominant pathogens (82.1%), while Gram-positive bacteria accounted for only 17.9%. *Klebsiella pneumoniae (ESBL (-)* and *ESBL (+))* and *Staphylococcus aureus MRSA (+)* were the most common bacteria, isolated in 35.9% and 14.0% of cases, respectively (Table 2).

3.4. Survival of neonates with sepsis

Table 3. Survival of neonates with sepsis (n=78)

Outcome			**Number (n)**	**Percent (%)**
Survival			65	83.3
Death	Early-onset sepsis	0	13	16.7
	Late- onset sepsis	13		

The neonatal sepsis mortality rate remained high (16.7%), with all deaths occurring in the late-onset sepsis group (Table 3).

3.5. The association between clinical and laboratory findings and neonatal sepsis treatment outcome

Table 4. Association of clinical findings with neonatal sepsis treatment outcomes using univariate analysis

Variables	**Outcome**	**Death (n = 13)**		**Survival (n = 65)**		**Odd Ratio (OR), 95% CI**	**p-value**
		n	**%**	**n**	**%**		
Gestational age (weeks)	<34	9	69.2	34	52.3	2.5 (0.7-8.8)	0.165
	≥34	4	30.8	31	44.7	1	
Birth weight (grams)	<1500	9	69.2	20	30.8	5.1 (1.4-18.4)	0.014
	≥1500	4	30.8	45	69.2	1	
Body temperature	Normal	9	69.2	39	60.0	1	
	Hypothermia	1	7.7	3	4.6	1.4 (0.1-15.6)	0.762
	Fever	3	23.1	23	35.4	0.6 (0.1-2.3)	0.426
Scleroderma	Yes	3	23.1	2	3.1	9.5 (1.4-63.8)	0.021
	No	10	76.9	63	96.9	1	
Petechiae	Yes	5	38.5	5	7.7	7.5 (1.8-31.7)	0.006
	No	8	61.5	60	92.3	1	
Cyanosis	Yes	3	23.1	3	4.6	6.2 (1.1-35.1)	0.039
	No	10	76.9	62	95.4	1	
Sepsis shock	Yes	5	38.5	8	12.3	4.5 (1.2-17.1)	0.029
	No	8	61.5	57	88.7	1	
Need mechanical ventilation	Yes	10	66.7	3	4.6	68.9 (12.2-390.2)	<0.001
	No	3	23.1	62	95.4	1	

Gastrointestinal bleeding	Yes	9	69.2	5	7.7	22.1 (5.2-94.0)	<0.001
	No	4	30.8	60	92.3	1	
Enlarged liver	Yes	3	23.1	2	3.1	9.5 (1.4-63.8)	0.021
	No	10	66.7	63	96.9	1	
Bulging fontanelle	Yes	1	7.7	4	6.2	1.3 (0.1-12.4)	0.837
	No	12	92.3	61	93.8		
Muscle tone	Normal	12	92.3	52	80.0	1	-
	Hypotonia	1	7.7	8	12.3	0.5 (0.1-4.8)	0.580
	Hypertonia	0	0.0	5	7.7	NA	

NA, not available.

Univariate regression analysis identified several factors significantly associated with mortality in neonates with sepsis, including: Birth weight <1500 grams, Scleroderma, cyanosis, septic shock, need for mechanical ventilation, gastrointestinal bleeding, hepatomegaly (p<0.05) (Table 4).

Table 5. Association of laboratory findings with neonatal sepsis treatment outcomes using univariate analysis

Variables	Outcome	Death (n = 13)		Survival (n = 65)		Odd Ratio (OR), 95% CI	p-value
		n	%	n	%		
White blood cells	4000-20000/mm^3	5	38.5	41	63.1	1	-
	<4000/mm^3	4	30.8	8	12.3	4.1 (0.9-18.7)	0.068
	>20000/mm^3	4	30.8	16	24.6	2.1 (0.5-8.6)	0.327
Low platelets	Yes	9	69.2	24	36.9	3.8 (1.1-13.8)	0.039
	No	4	30.8	41	63.1	1	
Elevated CRP	Yes	4	30.8	31	47.7	0.5 (0.1-1.7)	0.269
	No	9	69.2	34	52.3	1	
Glucose level	Normal	6	46.2	55	84.6	1	-
	Hypoglycemia	4	30.8	2	3.1	18.3 (2.8-122.0)	0.003
	Hyperglycemia	3	23.1	8	12.3	3.4 (0.7-16.6)	0.124
Gram-negative bacteria	Yes	11	84.6	53	81.5	1.2 (0.2-6.4)	0.792
	No	2	15.4	12	18.5	1	

Univariate regression analysis identified thrombocytopenia and hypoglycemia as significantly associated with mortality in neonates with sepsis (p<0.05) (Table 5).

Table 6. Multivariate analysis to identify factors associated with neonatal sepsis treatment outcomes

Variables		aOR	95% CI	p
Birth weight	≥1500 gram	1		
	<1500 gram	7.4	0.3- 196.5	0.229
Scleroderma	No	1		
	Yes	3.1	0.1-127.5	0.551

Cyanosis	No	1		
	Yes	31.2	0.5-1791.2	0.096
Sepsis shock	No	1		
	Yes	2.3	0.1-38.5	0.574
Mechanical ventilation	No	1		
	Yes	100.6	4.3-2370.7	0.004
Gastrointestinal bleeding	No	1		
	Yes	42.3	1.8-982.6	0.020
Enlarged liver	No	1		
	Yes	6.5	0.2-245.8	0.312
Low platelets <100000/mm^3	No	1		
	Yes	1.5	0.1-27.3	0.767

aOR, adjusted odds ratio; CI: Confidence Interval.

The multivariate regression analysis showed that neonates requiring mechanical ventilation and those with gastrointestinal bleeding had a significantly higher risk of mortality, with hazard ratios of 100.6 (95% CI: 4.3-2370.7, p=0.004) and 42.3 (95% CI: 1.8-982.6, p=0.02), respectively (Table 6).

4. DISCUSSION

Clinical and laboratory characteristics of neonatal sepsis

Worldwide, the incidence of early onset sepsis (EOS) in neonates tends to decrease owing to screening and treatment programs for maternal infections. However, late-onset sepsis (LOS) still accounts for a high proportion of neonatal morbidity owing to its association with invasive procedures after birth. Up to 69.2% of neonates in this study group underwent at least one invasive procedure (e.g., endotracheal intubation, umbilical venous catheter placement, gastric tube placement, and intravenous lines). Consistent with this, LOS was the predominant form of sepsis in our study, accounting for 92.3% of cases, compared to 7.7% for EOS. This trend is also common in many studies on neonatal sepsis in Vietnam and around the world, as evidenced by the work of Nguyen Duc Toan (2022) in Vietnam and Hind A. Alzahrani (2023) in Egypt [5, 6].

Many studies on neonatal sepsis have shown that clinical symptoms are diverse and multi-organ, and a neonate can have many symptoms [6-9]. Our study recorded the common clinical features of neonatal sepsis, including jaundice (64.1%), lethargy (60.3%), abdominal distension (57.7%), abnormal heart rate (50.0%), and fever (33.3%). In our study, 16.7% of the neonates had either respiratory failure requiring mechanical ventilation or septic shock.

In our study, 25.6% of neonates had leukocytosis (>20000/mm^3), whereas 15.4% had leukopenia (<4000/mm^3). Additionally, 43.6% of the patients presented with thrombocytopenia (<100000/mm^3). Other studies have also shown different trends in leukocyte and platelet count changes in neonatal sepsis [6, 8, 10]. This shows that the diagnostic value of leukocytes and platelets is not specific because the values of these indices may depend on several factors such as age and gestational age [2]. C-reactive protein (CRP) often increases later than other inflammatory markers and may increase due to non-infectious inflammatory processes, such as meconium aspiration, injury, and prolonged labor; therefore, so this parameter has low sensitivity for detecting early infection. However, in practice, monitoring serial CRP levels on subsequent days is valuable for assessing the treatment response. CRP levels increased by 44.9% in the neonates in this study. Disorders related to hyperglycemia, cytokine production, coagulation, acute dyslipidemia, and endothelial dysfunction can aggravate infectious diseases. In our study, 14.1% of the cases had hyperglycemia >10.0 mmol/L, similar to the study by Nguyen Duc Toan (2022) [6]. The pathogens isolated in our study were mainly gram-negative, and the two most common pathogens were *Klebsiella pneumonia* (35.9%) and *Streptococcus aureus* (16.6%). However, the distribution of this pathogen will depend on different time periods, neonatal units, countries [6-9], and surveying the pathogen in each unit will help direct appropriate and timely treatment at the facility and provide statistics on the trend of pathogens recorded in early

and late sepsis. Our study selected both early-onset and late-onset sepsis, with all cases of EOS caused by gram-negative bacteria. Consequently, the overall proportion of gram-negative bacteria was higher than that reported in other studies [6], [8]. In the study of Nguyen Duc Toan (2022), the incidence of Gram-negative bacteria was 32.3% and 67.8% of isolated bacteria were Gram-positive. The common gram-negative bacteria were *Klebsiella spp*. (7.1%), *Escherichia coli* (6.8%), and *Acinetobacter spp.* (4.0%), the common Gram-positive agents were *coagulase-negative staphylococci* (58.0%), *S. aureus* (4.5%) [6]. A study by Ba-Alwi NA (2022) in Tanzania noted that *S. aureus* and *Klebsiella* are also common pathogens and are associated with mortality in septic children with more than 40.0% of deaths caused by *S. aureus*, 38.0% by *Klebsiella* species, and 14.0% by *E. coli* [8].

Factors associated with neonatal sepsis mortality

The treatment results showed a recovery rate of 83.3% and mortality rate of 16.7%. These results are consistent with many domestic studies, such as those by Nguyen Duc Toan (2022) and Nguyen Ngoc Rang (2021) [6, 7]. However, these values are lower than those reported by Ba-Alwi NA (2022) in Tanzania, which reported a mortality rate of 45.4%, or Meshram RM (2019) in India, which reported a mortality rate of 38.2% [8, 11].

Newborns often have deficiencies in both humoral and cellular immunities. Passive antibodies transferred through the placenta, especially during the third trimester of pregnancy, play a key role in humoral immunity after birth. Therefore, very low birth weight (VLBW) neonates do not receive as much immune globulin from their mothers as full-term neonates. However, the functions of T cells and macrophages are deficient. As a result, the incidence of sepsis is often higher in neonates weighing less than 1500 grams [12]. Several previous studies have shown that the incidence of sepsis is higher in neonates weighing less than 1500 grams, and this is also associated with an increased risk of mortality compared to neonates weighing more than 1500 grams ($p<0.05$), as shown in the studies by Ba-Alwi NA (2022) and Meshram RM et al. (2019) [8, 11]. Our study found that neonates weighing less than 1500 grams had a 5.1 times higher risk of mortality than neonates weighing more than 1500 grams (OR= 5.1, 95%CI:1.4-18.4).

Our study identified several clinical manifestations in neonates with sepsis that predicted an increased risk of mortality, including scleroderma, cyanosis, gastrointestinal bleeding, hepatomegaly, septic shock, and the need for mechanical ventilation ($p<0.05$). Multivariate analysis showed that mechanical ventilation and gastrointestinal bleeding were independent risk factors for mortality in neonates with sepsis. In a study by Nguyen Duc Toan (2022), factors related to increased mortality included extremely preterm neonates, extremely low birth weight neonates, neonates with hypothermia, mechanical ventilation, hypotension, poor feeding, abdominal distension, scleroderma, thrombocytopenia, hyperglycemia, base excess <-20mEq/L, and increased serum lactate level ($p<0.05$). However, in multivariate analysis, scleroderma, leukopenia <4000/mm^3, thrombocytopenia <100000/mm^3, base excess <-20 mEq/L, and serum lactate >4 mmol/l were independent predictors of increased risk of death in neonates with sepsis ($p<0.05$) [6]. Meanwhile, a study by Ba-Alwi NA (2022) identified factors related to death in neonatal sepsis as low birth weight, vomiting, poor mobility, respiratory failure, need for mechanical ventilation, and gram-negative bacterial infection [8]. Meshram et al. (2019) noted that preterm birth, low birth weight, hypothermia, cyanosis, seizures, and prolonged capillary refill time were independent risk factors for death in neonatal sepsis ($p<0.05$) [11]. Neonates with sepsis who had septic shock or required mechanical ventilation had a significantly higher mortality rate than those without these complications. Septic shock is a life-threatening condition in which the circulatory system fails, leading to an inadequate oxygen supply throughout the body. If not promptly addressed, shock can rapidly lead to multiple organ failure and death, despite advancements in modern resuscitation techniques [13]. Similarly, neonates requiring invasive mechanical ventilation with intubation are often in critical condition, necessitating extended treatment, and consequently increasing their risk of hospital-acquired infections, particularly with multidrug-resistant bacteria, which significantly contributes to mortality in this population. In another hand, gastrointestinal bleeding could be a local lesion when the infectious agent invaded the intestinal mucosa, one of the factors contributing to complications of necrotizing enterocolitis, perforation, could also be a sign of coagulopathy, a severe manifestation of sepsis, and leading to high mortality in neonatal sepsis [2].

Thrombocytopenia, a low platelet count, is common in septic neonates. This is associated with damage to the reticuloendothelial system, which activates these cells, leading to increased platelet removal. Furthermore, thrombocytopenia in neonatal sepsis may be due to a low platelet count, high sequestration, destruction of platelets due to infection, direct cytotoxicity from bacterial

endotoxins, macrophage syndrome, and increased consumption in the setting of disseminated intravascular coagulation. Low platelet counts often occur late during sepsis and are associated with high mortality rate [13]. In our study, neonates with thrombocytopenia <100000/mm3 had a 3.8-fold higher risk of death than neonates without thrombocytopenia (p<0.05), like the results of Nguyen Duc Toan (2022) with OR=3.7 [6], Isabelle M. C. Ree (2017) also found that platelets below 150000/mm3 significantly increased the mortality rate in neonatal sepsis (OR=3.8) [14]. Severe and prolonged hypoglycemia in neonates can lead to irreversible cell dysfunction, organ failure, and eventually death [15]. Our study found that children with blood glucose level below 2.5 mmol/L had an 18.3-fold higher risk of death (OR=18.3; CI 95%: 2.8-122.0) than neonates without hypoglycemia, but this association was not statistically significant in multivariate analysis. Similarly, Gupta BK found an association between blood glucose abnormalities and mortality in neonatal sepsis [15]. The hypoglycemic group had a higher mortality rate (34.4%) than the normoglycemic group; however, this difference was not statistically significant. In contrast, the hyperglycemic group had a significantly higher mortality rate (58.3%) than the normoglycemic group (9.82%) (p<0.05).

Our study has some limitations. The sample size was relatively small, and data were collected from a single hospital. However, it could be seen that the patterns of pathogenic bacteria between developed and developing countries, and between different regions within each country, are not the same. This may be due to epidemiological factors, hospital strains, or infection control. Despite this, we observed a shift from early- to late-onset neonatal sepsis, highlighting the need for improved monitoring, early prediction, and prevention in neonatal care units to reduce the mortality rate in this population.

5. CONCLUSION

Neonates are more susceptible to late-onset sepsis, which manifests as diverse symptoms that affect various organs. Gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Staphylococcus aureus MRSA (+),* are the main culprits. Our study found a 16.7% mortality rate among neonates with sepsis. Mechanical ventilation and gastrointestinal bleeding were identified as the significant risk factors associated with mortality in this population.

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