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CLINICAL CHARACTERISTICS AND LABORATORY TEST IN FULL-TERM NEONATES WITH SEPSIS IN VIETNAM NATIONAL CHILDREN'S HOSPITAL (NORTHERN VIETNAM)

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Abstract. *Background*. Sepsis is a life-threatening condition in response to an infectious agent, causing damage to organs. Sepsis causes serious consequences in neonates due to high rates of mortality, sequelae, and disability. The Southeast Asian country of Vietnam features on of the highest infectious disease rates in the world (high rates of infection, disability and mortality), as well as being a middle-income country with a stratified health care system. The aim of this study was to evaluate the clinical and laboratory characteristics of patients at the Vietnam National Children's Hospital. *Materials and methods*. This descriptive study was conducted with 85 full-term infants with sepsis admitted to Vietnam National Children's Hospital in the period from December 2019 to April 2021. Patients had at least 2 clinical symptoms and 2 laboratory signs according to the criteria for assessment of neonatal sepsis (European Medicines Agency in 2010) along with positive blood culture results. *Results*. Common clinical symptoms in neonates with sepsis included poor feeding (89.4%), respiratory failure (69.4%), fever (51.8%), tachycardia (52.8%), and shock (25%). Anemic patients accounted for many (72.9%). Patients with increased white blood counts accounted for 41.2%. Newborns with a low white blood count accounted for 15.4%. Patients with thrombocytopenia were 49.6%. Most patients had elevated CRP (88.3%). The mean value of nCD64 was 10167.1±6136.9 molecules bound/cell. mHLA-DR was 9898.4±14173.9 molecules bound/cell. The Sepsis Index was 274.6±287.5. *Conclusions*. We recorded differences in clinical characteristics and laboratory tests in full-term neonates with sepsis at National Children's Hospital, of which, nCD64, mHLA-DR, and Sepsis Index should be further investigated and referred to as prospective routine biomarkers in diagnosis of neonatal sepsis.

Key words: *neonatal sepsis, nCD64, mHLA-DR, sepsis index, clinical symptoms, laboratory signs.*

КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА И ЛАБОРАТОРНЫЕ ИССЛЕДОВАНИЯ У ДОНОШЕННЫХ НОВОРОЖДЕННЫХ С СЕПСИСОМ ВО ВЬЕТНАМСКОЙ НАЦИОНАЛЬНОЙ ДЕТСКОЙ БОЛЬНИЦЕ (СЕВЕРНЫЙ ВЬЕТНАМ)

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Резюме. *Актуальность*. Сепсис — опасное для жизни состояние, развивающееся в ответ на инфекционный агент и вызывающее полиорганное поражение. Сепсис у новорожденных часто имеет тяжелые последствия, приводя к инвалидности, а нередко и к летальному исходу . Вьетнам, страна Юго-Восточной Азии, отличается

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одним из самых высоких показателей инфекционных заболеваний в мире (высокий уровень инфицирования, инвалидности и смертности), а также является страной со средним уровнем дохода и стратифицированной системой здравоохранения. Цель этого исследования состояла в том, чтобы оценить клинико-лабораторные характеристики пациентов с сепсисом во Вьетнамской национальной детской больнице. *Материалы и методы.* Описательное исследование было проведено с участием 85 доношенных новорожденных с сепсисом, поступивших во Вьетнамскую национальную детскую больницу в период с декабря 2019 г. по апрель 2021 г., имевших не менее 2 клинических симптомов и 2 лабораторных признаков в соответствии с критериями оценки неонатального сепсиса (Европейское агентство по лекарственным средствам, 2010 г.) в сочетании с положительными результатами посева крови. *Результаты.* Общие клинические симптомы у новорожденных с сепсисом включали вялое сосание (89,4%), дыхательную недостаточность (69,4%), лихорадку (51,8%), тахикардию (52,8%) и шок (25%). Преобладали больные с анемией (72,9%). Больные с повышенным содержанием лейкоцитов составили 41,2%, с пониженным содержанием лейкоцитов — 15,4%, с тромбоцитопенией — 49,6%. У большинства пациентов был повышен СРБ (88,3%). Среднее значение nCD64 составило 10167,1±6136,9 связанных молекул/клетку, mHLA-DR — 9898,4±14173,9 связанных молекул/клетку. Индекс сепсиса составил 274,6±287,5. *Выводы.* Нами обнаружены различия в клинических характеристиках и лабораторных показателях у доношенных новорожденных с сепсисом в Национальной детской больнице. Следует дополнительно исследовать показатели nCD64, mHLA-DR и индекс сепсиса, которые можно рассматривать как возможные рутинные биомаркеры в диагностике неонатального сепсиса.

Ключевые слова: *неонатальный сепсис, nCD64, mHLA-DR, индекс сепсиса, клинические симптомы, лабораторные признаки.*

Introduction

According to a report by the World Health Organization (WHO), in 2019 globally, there were 2.4 million infant deaths, of which neonatal sepsis is one of the leading causes [26]. Surveys conducted worldwide in the period 1990–2017 estimated there were more than 25 million cases of sepsis, mainly neonates [22]. Another study in 13 countries and territories from 1979 to 2019 also showed that the infant mortality rate was 17.6%, being higher in low- and middle-income countries [27]. Sepsis is a life-threatening condition in response to an infectious agent, causing damage to tissues and organs. Sepsis causes serious consequences in neonates due to high rates of mortality, sequelae, and disability [17, 27]. Vietnam is a country in Southeast Asia featuring some of the highest infectious disease rates in the world, including high rates of infection, disability, and mortality [22]. This prospective study aimed to evaluate the clinical and laboratory characteristics of patients at the Vietnam National Children'sHospital to show the clearest and most complete picture of full-term neonatal sepsisin NorthernVietnam.

Materials and methods

Patients. A descriptive study was conducted of 85 full-term infants admitted to the Neonatal Center of Vietnam National Children's Hospital in the period from 12/2019 to 4/2021.

Selection criteria: term newborns with at least 2 clinical symptoms and 2 laboratory signs according to the criteria for assessment of neonatal sepsis of the European Medicines Agency in 2010 (EMA 2010) [21] along with positive blood culture results.

Exclusion criteria: major congenital anomaly, inborn errors of metabolism, neonates who have received blood transfusion.

Laboratory tests. On the first day of admission, blood samples were taken for complete analysis of blood cells, blood gases, liver and kidney function, blood sugar, C-reactive protein, and blood culture by routine laboratory tests. Neutrophil CD64 (nCD64) and monocyte HLA-DR (mHLA-DR) expression were evaluated by flow cytometry (Becton Dickinson, Mountain View, CA, USA) using a phycoerythrin (PE) fluorescence quantification kit (QuantiBRITE PE, Becton Dickinson) and calculated into phycoerythrin molecules bound/cell. Sepsis Index (SI) was calculated from nCD64 and mHLA-DR values.

Statistical analysis. Results were analyzed with SPSS 20.0 statistical software (SPSS Inc, IL). The level of significance considered was 0.05. According to EMA 2010 criteria, we chosecut-offvalues for CRP, WBC and PLT of 15 mg/L, 20 000/mm^3 and 100 000/mm^3, respectively.

Ethics statement. Conduct of the study was approved by the Medical Research Ethics Committee at the Vietnam National Children's Hospital according to Decision No. 332 (dated March 10, 2020).

Results

In theperiod from December 2019 to April 2021 at the Neonatal Center in Vietnam National Children's Hospital, 85 patients with positive blood culture results met the research criteria. Among them, 39 were girls (45.9%), and 46 were boys (54.1%). Other features were:average gestational age 38.6±1.1 weeks; average weight 2918.2±548 grams; and age average hospital admission 10.4±8.2 days.

Most of the children received frontline treatment 78/85 (91.8%). The majority of children received frontline antibiotics 73/85 (85.9%) and frontline mechanical ventilation. Other characteristics were: 31/85 (36.5%) children had central catheters; 43/85

children were born by caesarean section; and 9/85 mothers had fever around delivery. Time of onset of infection: 52/85 children had early onset of infection (≤ 7 days); 33/85 children had late onset of infection (> 7 days).

Discussion

Currently, the trend of early neonatal sepsis is decreasing, and the rate of late neonatal sepsis is increasing. A. van den Hoogen tracked data from 1978–2006. The rate of early sepsis decreased from 52.1% to 28.1%. In contrast, the rate of late sepsis increased from 11.4% to 13.9% [25]. This may be due to better management of pregnancy, the mother are vaccinated against Group B streptococcus avoid infecting the baby, ormaternalinfections are better managed.

The rate of children with fever accounted for 51.8%. Our results are similar to the results of A Sorsa in Ethiopia with the rate of 47.5% of full-term infants with sepsis having fever, but higher than the rate of 23.9% of infants with febrile illness in J. Davis's study [3, 23]. The rate of febrile children with severe infections (septicemia, meningitis, etc.) ranged from 6.3% to 28% [8].

Our rate of children with hypoxemia was higher than that of A. Sorsa (34%) [23]. In our study, 21.2% of children with rales showed damage due to bronchopneumonia or pneumonia, so many children had rapid breathing.

Tachycardia is the most common symptom (51.8%), especially in $^1/_3$ children with septic shock and capillary refill times > 3 seconds. Tachycardia is a common finding in neonatal sepsis, but is not specific. In our study, many children's fever may be the cause affecting the rate of tachycardia. Poor perfusion and hypotension are often detected late. The rate of these two symptoms in our study was 25/85 (29.4%), equivalent to the research results of B.J. Stoll [24].

Poor feeding was the most common digestive symptom, accounting for 92.9%. Abdominal distention and diarrhea accounted for 43.5% and 2.4%. The study of M.S. Edwards showed that gastrointestinal symptoms presented with the rates of: jaundice 35%, hepatomegaly 33%, poor appetite 28%, vomiting 25%, abdominal distention 17%, and diarrhea 11% [6].

Table 1. Clinical characteristics of the study group (n = 85)

Parameter	Number	Percentage
Rapid breathing	30	35.3
Apnea > 20 seconds	4	4.7
SpO_2 < 85%	64	75.3
Rales	18	21.2
Tachycardia	44	51.8
Shock	24	29.4
Refill > 3 seconds	25	29.4
Mottled skin	19	22.4
Oliguria	15	17.6
Hypotension	13	15.3
Poor sucking	79	92.9
Delayed gastric emptying	60	70.6
Abdomen distention	37	43.5
Diarrhea	2	2.4
Lethargy	25	29.4
Seizures	2	2.4
Hypertonic	2	2.4
Hypotonic	1	1.2
Scleroderma	17	20.0
Petechiae	15	17.6
Jaundice	10	11.8
Abscess	3	3.5
Boil	3	3.5
Skin necrosis	2	2.4
Rash	2	2.4
Purulent dermatitis	1	1.2

Neurological symptoms in our study were mainly lethargy. In V. Anand's study, 38% of neonates with sepsis had seizures [1]. L. Pugni, evaluating a group of neonates with severe sepsis, showed common neurological symptoms including 56% hypotonicity, 56% lethargy, and 3.9% seizures [19].

The mean Hct of the study group was 40.3±7.3%, and 72.9% of children were anemic. Our rate of children with anemia is lower than that of N. Cai (84.9%) [2]. Anemia is one of the common conditions in neonatal sepsis.

Table 2. Peripheral blood count and CRP (n = 85)

Parameter	X±SD	Increase (n, %)	Decrease (n, %)	Normal (n, %)
White blood cell, × 10^9 cells/L	16.78±10.31 (2.15–54.98)	35 (41.2)	13 (15.4)	37 (43.5)
Platelet, × 10^9 cells/L	21.17±20.44 (4–77.3)	0	42 (49.6)	43 (50.4)
Hct, %	40.3±7.3	23 (27.1)	62 (72.9)	0
CRP, mg/L	84.2±76.8	75 (88.3)	0	10 (11.7)

Table 3. Coagulation (n = 80)

	X±SD	Increased (n, %)	Reduced (n, %)	Normal (n, %)
Prothrombin, %	65.5±26.2	0 (0.0)	48 (60)	32 (40)
APTT, second	47.5±23.3	46 (57.2)		34 (42.8)
Fib, second	3.5±1.5	40 (50)		40 (50)

Table 4. Blood biochemical index (n = 85)

	X±SD (mmol/L)	Increased (n, %)	Reduced (n, %)	Normal (n, %)
Na^+	134.3±5.2	5 (4.6)	42 (50.1)	38 (45.3)
K^+	4.6±1.4	33 (38.2)	8 (9.5)	44 (52.3)
Glucose	5.6±5.1	20 (23.6)	2 (2.3)	63 (74.1)
GOT	511.7±185.3	39 (45.2)		46 (54.8)
GPT	272.2±89.6	18 (20.6)		67 (79.4)
Urea	29.5±5.1	18 (20.6)		67 (79.4)
Creatinin	76.7±42.8	25 (28.8)		60 (71.2)
Albumin	7.9±6.6	50 (58.8)		35 (41.2)

Table 5. Blood gas indices (n = 51)

	X±SD (mmol/L)	Increased (n, %)	Reduced (n, %)	Normal (n, %)
pH	7.4±1.24	1 (2.0)	35 (68.6)	15 (29.4)
BE	–6.8±8.1		24 (74.1)	27 (25.9)
Lactate	5.1±3.7	46 (90.1)		5 (9.9)

Our study showed 41.2% of children with increased white blood cells (> 20×10^9 cells/L) and 15.4% of children with reduced white blood cells (< 4×10^9 cells/L). Newman and Hornik showed that low white blood cell counts were more strongly associated with early sepsis in premature infants than in term infants, especially after 4 hours of age. The author also found that white blood cell counts have diagnostic value in early-onset sepsis rather than late-onset [10, 15].

Platelet values in our results were higher than in the study of I.M.C. Ree. The proportion of children with platelets < 150×10^9 cells/L accounted for 49%. Platelet reduction < 100×10^9 cells/L accounted for 39%. The rate of platelets < 150×10^9/L in neonatal sepsis due to Gram-negative bacteria was 69%. For Gram-positive bacteria it was 47% [20].

The average CRP concentration was 84.2± 76.8 mg/L. Most patients had CRP increased above 15 mg/L (88.3%). The study of A. Sorsa showed that CRP > 20 mg/L increased the risk of sepsis by 5.7-fold compared with the group with negative blood cultures [23]. However, J.R. Delanghe suggested that CRP has low sensitivity to detect early-onset sepsis due to the physiological increase in CRP in 3 days postpartum [4]. Elevated CRP may also be caused by non-infectious inflammatory processes, such as meconium aspiration. Therefore, CRP should be combined with other indices (such as nCD64, IL-6 or IL-8) to increase diagnostic value.

In our study, 60% of children had low prothrombin. Coagulation disorder is a serious and common complication in neonatal sepsis. We had a low rate of children with severe electrolyte disturbances (Na^+ < 125 mmol/L, K^+ > 14.2 mmol/L). These were cases of septic shock and death. Research by M.S. Ahmad on a group of neonates with septic shock showed that the rate of children with electrolyte disorders was up to 75.5%; hyperkalemia was the most common electrolyte disorder (39%). The author also showed a strong association between electrolyte disturbances and mortality in children, wherein all children who died had electrolyte disturbances [4].

We also encountered a low rate of children with renal failure with urea > 200 mmol/L and liver damage with GOT > 2000 UI/L. The study of N.B. Mathur showed that the rate of acute renal failure in neonate with septicemia was 6,5%, and the mortality rate of acute renal failure was 30.7% [12].

Most children had mild metabolic acidosis, but the range was also very wide with: pH = 7.24±1.24 (6.91–7.46) and BE = –6.8±8.1 mEq/L (–22–15). Children with severe metabolic acidosis (pH < 7) and disturbances in major blood gas indices (lactate > 15) are children with unrecoverable septic shock. Blood gas abnormalities are common in neonates treated in the neonatal intensive care unit and are associated with increased mortality. The study by M. Mohammad Yusuf showed that: the mortality group had a lower blood pH (7.3±0.19) than the alive group (7.36±0.1); and the BE of the mortality group was lower (–10.74±15.89 mmol/L) than the live group (–4.3±6.88 mmol/L) [14].

nCD64 had an average value of 10167.1 molecules bound/cell in our study. N. Efe Iris studied adult patients and showed that the sepsis group had an average nCD64 index of 8006 molecules bound/cell, significantly higher than the control group (average nCD64 of 2786 molecules bound/cell). The cut-off value of nCD64 of 2500 molecules bound/cell is considered to have diagnostic value for sepsis in adults, with a sensitivity of 94.1% [7]. P.C. Ng's study showed that the value of nCD64 was not high. The averages in the neonate infected group at the 1st and 24th hour were: 8320 molecules bound/cell and 9704 molecules bound/cell, respectively. These werehigher

Table 6. nCD64, mHLA-DR, and Sepsis Index (n = 85)

Index	X±SD
nCD64 (ABC)	10 167.1±6136.9 (1198–32 965)
mHLA-DR (ABC)	9898.4±14 173.9 (434–96 881)
Sepsis Index	274.6±287.5 (18.7–1376.8)

Note. ABC — aantibody-phycoerythrin molecules bound/cell.

than the non-infected group for the1sthour and 24th hour: 3915 molecules bound/celland 4491 molecules bound/cell, respectively.

In the control group (healthy children), nCD64 had an average value of 3426 molecules bound/cell [16]. The nCD64 valuesin premature infants were also very different in the sepsis group, non-sepsis group, and healthy children in J. Du's study. The sepsis group had an average nCD64 of 2869.67 molecules bound/cell, while the healthy group of children had an average of 1610.80 molecules bound/cell ($p = 0.0001$) [5].

mHAL-DR had an average value of 9898.4 molecules bound/cell, equivalent to 32.4% of the value of healthy children. In the study of T.F. Manzoli, areduction in mHLA-DR (< 30% compared with the control group) was a predictor of mortality in the first week of admission [11]. C. Meisel showed that all patients with severe sepsis had mHLA-DR < 8000 molecules bound/cell [13]. S. Tamulyte's study determined that mHLA-DR thresholds (≤ 8000/≤ 5000/≤ 2000 molecules bound/cell) are levels that predict the severity of the patient's condition independent of disease etiology. mHLA-DR values of 2000 molecules bound/cell and 5000 molecules bound/cell were predictive of: longer stay in the intensive care unit; duration of mechanical ventilation and antibiotic therapy; as well as higher microbiological pathogen concentrations.

In our study, the sepsis index (SI) had an average value of 274.6±287.5 (18.7–1376.8). S. Goswami's study of nCD64 and mHLA-DR by mean fluorescence concentration (MFI) also showed that nCD64 was significantly increased in the sepsis group compared with the healthy group ($p < 0.05$), but mHLA-DR was decreased. We found significant difference in the sepsis group and the non-infectious group [9]. The mean value of SI in the group of adult patients with trauma of Ngoc Thao was 112.95 (46.16–270.66). Our results are higher because our patients are full-term infants [18].

Conclusion

In summary, we found that common clinical symptoms in neonates with sepsis included poor feeding (89.4%), respiratory failure (69.4%), fever (51.8%), tachycardia (52.8%), shock (25%), and anemic (72.9%). Increased white blood count accounted for 41.2%; low white blood count accounted for 15.4%. In patients, 49.6% had thrombocytopenia. Most patients had elevated CRP (88.3%). The mean value of nCD64 was 10 167.1±6136.9 molecules bound/cell. mHLA-DR was 9898.4±14 173.9 molecules bound/cell. Sepsis Index was 274.6±287.5.

Conflict of interest

We declare that we have no conflict of interest.

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