MINISTRY OF EDUCATION TRAINING MINISTRY OF HEALTH
NATIONAL INSTITUTE OF MALARIOLOGY PARASITOLOGY AND ENTOMOLOGY

CLINICAL CHARACTERISTICS LABORATORY TESTS AND OUTCOMES IN FULL-TERM NEONATES WITH SEPSIS IN NATIONAL CHILDREN'S HOSPITAL (2019-2021)

Major : Infectious and tropical diseases

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PH.D THESIS SUMMARY

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ABBREVIATION

Abbreviation	Meaning
AIDS	Acquired Immuno Deficiency Syndrom
APTT	Activated Partial Thromboplastin Time
AUC	Area Under the Curve
CD	Cluster Differentiation
CRP	C – Reactive Protein
DNT	
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicines Agency
Fib	Fibrinogen
HFO	High Frequency Oscillatory
HIV	Human Immuno-deficiency Virus
I/T	Immature to Total neutrophil ratio
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
mHLA-DR	mono Human Leucocyte Antigen – DR
MIC	Minimum Inhibitory Concentration
nCD64	neutrophil CD64
PCR	Polymerase Chain Reaction
PT	Prothrombin Time
SD	Standart Deviation
SI	Sepsis Index
ROC	Receiver Operating Characteristic
TNF	Tumor Necrosis Factor
WHO	World health Organization

LIST OF RESEARCH WORKS RELATED TO THE THESIS TO BE PUBLISHED

1. Nguyen Thi Ngoc Tu, Le Thanh Hai, Truong Thi Mai Hong, Pham Thu Hien, Le Thi Ha, Doan Thi Mai Thanh (2020), nCD64, mHLA-DR: Sensitive Diagnostic Markers of Infection in Term Infants Receiving Antibiotic Treatment, *Sys Rev Pharm 2020; 11(9): 1077-1081*.
2. Nguyen Thi Ngoc Tu, Truong Thi Mai Hong, Le Ngoc Duy, Le Thi Ha (2022).Evaluation of results of treatment of full-term neonatal sepsis at the National Childrens's Hospital (2019-2021) and some related factors, *Journal of Community Medicine*, Vol. 63, No. 2.

INTRODUCTION

According to a report by the World Health Organization (WHO), in 2019 globally, 2.4 million infants died. Among them, sepsis is the leading cause of neonatal mortality. Sepsis is a life-threatening condition in which the body's response to an infectious agent causes damage to tissues and organs.

Recently, cell surface marker 64 on neutrophils (nCD64) and human leukocyte antigen DR type on monocytes (mHLA-DR) have been shown to be very important in the diagnosis of sepsis in newbornss.

Currently, the treatment of neonatal sepsis is still facing many difficulties due to late diagnosis, the choice of antibiotics that are not suitable for the pathogen model has changed a lot. Sepsis has always been a group of diseases accounting for a high proportion in the neonatal morbidity model. At the National Newborns's Hospital, the manifestations of the disease have changed due to the influence of previous interventions and treatments. Therefore, we pose the question: What is the clinical and laboratory picture of sepsis in full-term neonates at the National Children's Hospital today? In particular, are the nCD64 and mHLA-DR indices valuable in the diagnosis of neonatal sepsis? What is the effectiveness of the current neonatal sepsis treatment regimen at the National Children 's Hospital?

Therefore, we carried out the research topic: "Clinical characteristics, laboratory tests and results of treatment of full-term neonatal sepsis at the National Children's Hospital (2019 - 2021)"

The objectives of the study are:

1. Describe some clinical and subclinical characteristics of sepsis in full-term neonates at the National Children's Hospital (2019-2021).

2. Determination and antibiotic sensitivity of some common agents causing neonatal sepsis.

3. Evaluation of results of neonatal sepsis treatment at the National Children's Hospital (2019 – 2021).

NOVELTY AND SCIENTIFICANCE OF THE THESIS

General study on the entire clinical picture, subclinical, common pathogens and treatment results of the disease with high mortality and disability rate is neonatal sepsis. The study provided evidence on the prevalence of common symptoms, laboratory changes in neonatal sepsis, and treatment outcomes. The study also showed the pattern and antibiotic sensitivity of common pathogenic microorganisms at the National Children's Hospital and evaluates the effectiveness of the treatment regimen being applied at the leading hospital specializing in Pediatrics. The datas recorded from clinical examination and laboratories was valuable scientific evidence as a basis for understanding factors related to neonatal sepsis, disease prognosis and

proposing measures prevention reduced morbidity and mortality. At the same time, the results of the study also contributed to providing information and experience for neonatologists at the National Children's Hospital and training for grassroots medical levels and provincial hospitals.

This is the first study to use some novel immunoassays such as nCD64, mHLA-DR, SI and showed the value of these tests in diagnosing neonatal sepsis compared with previous tests. From the results of the study, these immune markers can be applied to support early and more accurate diagnosis of neonatal sepsis.

STRUCTURE OF THE THESIS

The thesis is 129 pages thick, including: Introduction: 2 pages; Overview: 32 pages; Objects and research methods 24 pages; Research results 38 pages; Discussion: 30 pages; Conclusion 2 pages; Recommendation 1 page. The thesis has 12 figures, 50 tables of data, 5 appendices. There are 129 references, there are > 50% of references in the last 5 years.

Chapter 1
LITERATURE REVIEW

1.1. Outline of neonatal sepsis

1.1.2. Some concepts of sepsis in term neonates

Neonatal sepsis: An infection that occurs within the first 28 days after birth.

Neonatal sepsis is classified according to the time of onset of infection: Early when clinical symptoms appear within 72 hours of birth; late: after 72 hours.

Neonatal sepsis is a systemic condition involving hemodynamic changes or other clinical manifestations that can lead to serious injury and death due to micro-organisms such as bacteria, viruses, yeast.

- Newborns is a child counted from birth to the end of the 28th day after birth. Newbornss are full term when gestational age is from 37 weeks to 42 weeks, premature birth is less than 37 weeks, old months are over 42 weeks.

1.3. Incidence of neonatal sepsis in the world and in Vietnam

Statusof neonatal sepsis in the world

Neonatal sepsis has a high prevalence in neonatal morbidity patterns, especially in developing countries. In Georgia in 2009, neonatal sepsis accounted for 20% of all hospital admissions and 53% of infants treated in neonatal intensive care units. In South Africa in 2012, the neonatal infection rate was 10,6/1000 live births, the neonatal mortality rate due to neonatal sepsis was 2.3/1000 live births. In India in 2016, the neonatal infection rate was 6,7/1000 live births. In Italy in 2016, the neonatal morbidity and neonatal mortality rates due to neonatal infections were 0,61 and 0,08/1000 live births,

respectively. In Switzerland, in the period 2011-2015, the rate of newbornss with neonatal sepsis was 146/100,000 live births.

Status of neonatal sepsis in Vietnam

In 2003, at the neonatal intensive care unit of the National Children's Hospital, the rate of neonatal infections was 2,1%, of which 61 newborns died (68,7%). In 2016, Tran Dieu Linh described the clinical and subclinical characteristics of neonatal sepsis in term infants born by caesarean section. In 2017, Vo Huu Hoi studied the characteristics of blood clotting disorders and related factors of neonates with sepsis. In 2021, Thai Bang Giang described the bacterial infection characteristics of patients with fungal infections at the National Children's Hospital and the prophylactic effect of the antifungal drug fluconazole on premature infants.

Study on the causative agent of neonatal sepsis

In 2011, at the Vietnam - Cuba Friendship Hospital in Dong Hoi, *Citrobacte*r was the leading cause (52.83%), *S. aureus* accounted for 28,30%, *E. coli* accounted for 7,55% and *Enterobacter* accounted for 7,55%. Research in 2013 by Le Kien Ngai showed that *E. coli* was the leading cause of neonatal sepsis at the National Children's Hospital. At Hai Phong Newborns's Hospital in 2017, the rate of neonatal infections caused by *K. pneumonia* accounted for 35.7%, *Acinetorbacter* accounted for 28,6%. *E. coli* accounted for 7,1%, *S. aerius*accounted for 14,3%. Thus, the cause of sepsis was mainly Gram-negative bacteria. In 2020, at the National Hospital of Obstetrics and Gynecology, *Coagulase-negative staphylococci (CoNS)* accounted for 27,5%. *S. marcescens* caused 32.3% of late infections, fungi accounted for 1,6%. In 2015-2016, at the National Newborns's Hospital, the rate of fungal infections was 1,2%, of which the rate was mainly blood fungus with the rate of 85,7%.

Study on antibiotic resistance of bacteria

From 2003 to 2004, *P. seudomonas* was resistant to most antibiotics, only sensitive to amikacin. At the National Children's Hospital in 2017, penicillin was resistant to a very high rate (87,5%). Ceftriaxone is resistant with the rate of 21,57%. Levofloxaxin and ciprofloxaxin were resistant to drugs at 5,13% and 10,34%, respectively. *E. coli* was resistant to levofloxaxin and ciprofloxacin with the rate of 60% and 50.1%, respectively. At the National Hospital of Obstetrics and Gynecology (2018-2019), all strains of *S. marcescens*, *E. coli* and *K. pneumoniae* were resistant to penicillin group antibiotics. The rate of *E. coli* bacteria resistant to aminoglycoside antibiotics was the lowest. The rate of resistance of *S. marcescens* and *K. pneumoniae* to carbapenem antibiotics is over 60%.

1.4. Clinical and laboratory features of sepsis in term neonates

1.4.1. Clinical features of sepsis in term neonates

- Before birth: fetal heart rate is fast, amniotic fluid is dirty, amniotic fluid contains meconium.

- Right after birth: Low apgar score.

- Temperature disorders: The body temperature of infants with sepsis may increase, decrease or be normal.

- Respiratory symptoms: Rapid breathing, groaning, rising and falling of the nostrils, using accessory muscles of respiration)

- Circulatory symptoms: Tachycardia > 160 beats/min, hypoperfusion, capillary refill time > 3 seconds and hypotension, circulatory failure, shock.

- Neurological symptoms: Lethargy, decreased muscle tone, poor appetite, irritability, convulsions.

- Other symptoms: jaundice, hepatomegaly, poor feeding, vomiting, abdominal distension, diarrhea.

1.4.2. Laboratory tests

Blood culture: The gold standard for diagnosing neonatal sepsis but the false negative rate is high.

Cerebrospinal fluid test: Gram stain, culture, cell count, glucose, protein. CSF results are assessed according to birth weight, gestational age, and actual age of the child.

Complete blood count: White blood cells and platelets may be increased, decreased, or unchanged. Newborns may be anemic.

C-reactive protein (C-reactive protein): Usually elevated.

nCD64 - neutrophil CD64: During infection, neutrophil will be activated so the number of CD64 receptors will increase significantly

mHLA-DR: In healthy subjects, monocytes express >90% of HLA-DR. In bacterial infections, mHLA-DR is decreased.

SI: Sepsis index

$$\mathrm{SI} = \frac{\mathrm{nCD64\ x\ 100}}{\mathrm{mHLA-DR}}$$

SI has moderate sensitivity and specificity for the diagnosis of neonatal sepsis and has predictive value in mortality in patients with severe neonatal sepsis within 30 days.

1.5. Diagnosis of neonatal sepsis

- Confirmed diagnosis: Infectious patients with positive blood culture results.

- Differential diagnosis: With viral infections, non-inflammatory diseases have respiratory, circulatory, and neurological manifestations.

1.6. Treatment of neonatal sepsis

- Infusion therapy in the treatment of neonatal septic shock

- Use of cardiac and vasoactive drugs

- Airway support

- Antibiotic therapy

Depending on the causative agent, the duration of antibiotic use may vary, at least 10 days. When antibiogram results are not available, broad-spectrum

antibiotics are used to treat the most common bacteria. The most common antibiotic combinations are β-lactams and aminoglycosides. Vancomycin, which can be substituted for ampicillin in the treatment of Gram-positive bacteria.

- Other measures: Continuous hemodialysis, extracorporeal membrane oxygenation (ECMO).

Chapter 2
STUDY SUBJECTS AND METHODS

2.1. Objective 1: Describe some clinical characteristics, laboratory tests of sepsis in full-term neonates at the National Children's Hospital (2019 - 2021).

2.1.1. Subjects

Neonates with ≥ 2 clinical manifestations along with ≥ 2 laboratory signs according to the European Medicines Agency (EMA 2010) UTI assessment criteria and positive blood culture results.

Selection criteria: Patients with ≥ 2 clinical manifestations and ≥ 2 subclinical signs and positive blood culture results.

Exclusion criteria

- Patients received blood transfusions or blood products before conducting the study.
- Patients with severe congenital diseases affecting life function.
- The child's parents or guardians did not consent to participate in the study

2.1.2. Site of the study: The study was conducted at the National Children's Hospital.

2.1.3. Time of the study: The study was carried out from December 1, 2019 to April 30, 2021.

2.1.4. Study design

2.1.4.1. Methods: Description of the case series

2.1.4.2. Sample size and sample selection

Apply the estimation formula to a ratio

$$n = Z^2_{1-\alpha/2} \frac{(1-p)}{p\varepsilon^2}$$

n: Minimum sample size

p: Rate of arrhythmia symptoms in newborns with sepsis. We choice p = 0,05 (according to the study of Nguyen Nhu Tan).

Z1-α/2: Confidence coefficient, for 95% confidence, then Z1-α/2 = 1.96

ε: Desired relative error. Choose ε = 0.2

With the selected values, the calculated sample size is 79 newborns.In fact, we selected 85 neonates with positive blood cultures, which met the study criteria.

2.2. Research scope

- Epidemiological characteristics: To determine the distribution of epidemiological characteristics of the disease such as age, gender, mother's medical and maternity history, birth history, child's history of frontline treatment...

- Clinical features: Determine the distribution of symptoms of the disease.

- Laboratory test: Blood count, immunological index, blood biochemistry, cerebrospinal fluid

- Time of assessment: The first visit recorded patients who met the study criteria.

2.3. Objective 2: Determine and antibiotic sensitivity of common pathogens causing neonatal sepsis at the National Children's Hospital.

2.3.1. Study subjects

Study subjects:

- Microorganisms were identified in the patient's blood sample.

- The sensitivity of the antibiotic to microorganisms in the blood sample.

Exclusion Criteria: Specimens that do not meet laboratory standards.

2.3.2. Site of study: Neonatal Center, Department of Microbiology at National Children's Hospital.

2.3.3. Time of studay: The study was carried out from December 1, 2019 to April 30, 2021.

2.3.4. Stuy design

- Research methods: Descriptive study, experimental analysis.

- Sample size: All blood samples have identified pathogens.

2.3.5. Research scope

- Determine the cause of the disease: Identify microorganisms from positive samples by culture method.

- Determination of susceptibility and resistance of microorganisms in cultures that were positive for antibiotics commonly used in disease treatment.

2.4. Objective 3: Evaluate the results of neonatal sepsis treatment.

2.4.1. Study subjects

Selection criteria: Full-term infants from 1 to 28 days old diagnosed with sepsis were treated at the Neonatal Center - National Children's Hospital during the study period according to the unified protocol.

Exclusion criteria: The patient's parents or guardians did not consent to participate in the study.

2.4.2. Site of the study: Neonatal Center - National Children's Hospital.

2.4.3. Time of the study: From December 1, 2019 to April 30, 2021.

2.4.4. Study design

- Method: Clinical intervention method with before - after assessment.

- Sampling: Select all neonatal patients, diagnosed with neonatal sepsis, identified pathogenic microorganisms treated according to a unified protocol of

the Newborns Specialist Training Program of the Maternal Care Network and Newborns West Midlands 2019 at the National Children's Hospital during the time of the study.

2.4.5. Research scope

- Indicate treatment according to a uniform regimen for all patients
- Calculate the rate of cure, sequelae, and death at the time of discharge of the whole patient group according to the time of disease onset and the cause of the disease.
- Duration of treatment: Average number of days of treatment, average of treatment results, etiology, time of disease onset...
- Interventional procedures: The rate of surgical interventions according to treatment results.
- Treatment drugs: Number of antibiotics to be used, rate of transfusion of blood products: red blood cells, platelets, fresh plasma...
- Evaluation of some factors related to the outcome of disease treatment.

2.5. Techniques used in the study

Clinical symptoms are recorded when at least 2 doctors specializing in neonatology of the Center for Neonatology - National Children's Hospital.

2.6. Tools used in the study

Medical records: Appendix 4

2.7. Error, noise and control method

- Errors caused by caregivers not remembering enough information: experienced doctors ask patients many times and ask the kinds of questions that help recall.
- Errors when performing tests: Tests are performed with a unified process on a highly automated system, under the supervision of the heads of the units.
- Newborns who were discharged from hospital, asked to stop treatment, died: assessed by 02 neonatologists.

2.8. Data processing methods

- Data after being collected according to the research medical record form will be coded, entered and analyzed using SPSS 22.0 software.
- Descriptive statistics includes calculating the frequency and proportion of qualitative variables and calculating the mean and median of the quantitative variables. The chi-square test is used to compare ratios. The T-student, Anova test is used to compare means, or medians. The difference was considered statistically significant when $p < 0.05$. Based on the ROC (Receiver Operating Characteristic) curve to determine the cut-off point and the sensitivity and specificity of the test indicators nCD64, mHLA-DR, SI. Odds ratio OR (Odd ratio) was calculated to find out the correlation between outcome variables and patient characteristics with significance level $\alpha=0.05$ and 95% confidence interval.

2.9. Ethics in research

The conduct of the study was approved by the Ethics Council in Medical Research at the National Children's Hospital according to Decision No. 332/BVNTW-VNCSKTE dated March 18, 2020.

Chapter 3.
RESULTS

At the National Children's Hospital, we have collected 85 patients who met the study criteria.

Male newborns had 46 cases, accounting for 54.1%. Female newborns accounted for 45.9% with 39 cases. The gestational age of the newborns admitted to the hospital was the lowest at 37 weeks, the highest at 41 weeks (38.5 ± 1.1 weeks), the average weight was 2918.2 ± 548 grams, the mean age at admission was 10.4 ± 8, 2 days. The majority of newborns received first-line treatment (91.8%), using antibiotics before being hospitalized (85.9%). At the frontline, 45 newborns were mechanically ventilated (52.9%), and 31 newborns had central catheters (36.5%). There were 55 newborns who had peripheral venous placement (64.7%).

3.1. Clinical and laboratory test of sepsis at term neonates

There were 52 newborns showing early infection (61.2%) and 33 newborns showing late infection (38.8%). The difference in the time of onset of infection was statistically significant ($p < 0.05$). Patients with fever accounted for a high percentage (51.8%). There were 6 cases of hypothermia (7%).

Table 3.7. Respiratory characteristics of newborns (n=85)

Symptoms	Number	%
Rapid breathing	30	35,3
Apnea > 20 seconds	4	4,7
SpO_2 < 85 %	64	75,3
Rales	18	21,2
Respiratory support		
Spontanous breath	26	30,6
Oxygen	29	34,1
Mechanical ventolation	30	35,3
Total	85	100

Only 30.6% of newborns breathed on their own, most of them had respiratory failure and required oxygen or mechanical ventilation (69,4%). There are 21,2% of patients with pulmonary rales.

Table 3.8.Circulatory symptoms in newborns (n=85)

Symptoms	Number	%
Tachycardia	44	51,8
Shock	25	29,4
Refill > 3 seconds	25	29,4
Mottled skin	19	22,4
Oliguria	15	17,6
Hypotension	13	15,3

Patients with tachycardia accounted for 51,8%. There were 29,4% babies in shock. All patients with shock received vasopressors at the time of diagnosis.

Table 3.9. Patient's digestive symptoms (n=85)

Symptoms	Number	%
Poor sucking	79	92,9
Delayed gastric emptying	60	70,6
Abdomen distention	37	43,5
Hepatomegaly	8	9,4
Vomit	4	4,7
Diarrhea	2	2,4
Spengatomegaly	1	1,2
Nutrition		
TPN	43	50,6
Oral	32	37,6
Apart TPN	10	11,8
Total	85	100

The majority of babies suckled poorly (92,9%). There were 43,5% patients with abdominal distension, 2,4% patients with diarrhea. There were 8 patients with enlarged liver (9,4%). The main form of nutrition is complete parenteral nutrition (50,6%) and oral (37,6%).

Table 3.10. Patient's neurological symptoms (n=85)

Symptoms	Number	
Lethargy	25	29,4
sticmulate	10	11,8
Seizures	2	2,4
Hypertonic	2	2,4
Hypotonic	1	1,2
No symptoms	45	52,8
Total	85	100

There were 29,4% lethargic babies, 11,8% excited. There are 2 babies with seizures, 2 patients with increased muscle tone.

3.11. Skin and mucosal symptoms of patients (n=85)

Symptoms	Number	%
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
No symptom	32	37,6
Total	85	100

Scleroderma was the most common skin symptom (20%). Subcutaneous hemorrhage and jaundice accounted for 17,6% and 11,7%, respectively.

3.1.3. Laboratory test of patients

Table 3.12: Peripheral blood Hct concentration (n=85)

Index	X± SD Hct ± SD (%)	Anemia (Hct <45%) (n, %)	Normal Hct ≥ 45% (n, %)
General (n=85)	40,3 ± 7,3	62 (72,9)	23 (27,1)
According to the group cause of the disease			
Gram (+) (n= 33)	42,1 ± 5,9	21 (63,6)	12 (36,4)
Gram (-) (n=44)	39,8 ± 7,2	35 (79,5)	9 (20,5)
Fungi (n = 8)	36,1 ± 11,2	6 (75)	2 (25)
According to the cause of the disease			
S. aureus (n=24)	42,2 ± 6,1	14 (58,3)	10 (41,7)
K.pneumonia (n=14)	41,4 ± 8,1	10 (71,4)	4 (28,6)
E.coli (n=14)	40,3 ± 7,4	12 (85,7)	2 (14,3)
S. agalactiae (n=7)	42,1 ± 6,8	2 (28,5)	5 (71,5)
Nấm Candida (n=8)	36,1 ± 11,2	6 (75)	2 (25)
Khác (n=18)	40,6 ± 6,2	18 (100)	0

The mean Hct concentration of the study group was 40,3 ± 7,3%. Anemic newborns accounted for a high rate (72,9%).

Table 3.13. Peripheral blood white blood cell count (n=85)

Index	X± SD (10^9 cells/L)	Increase (n,%)	Reduce (n, %)	Normal (n,%)
General (n=85)	16,78 ± 10,31 (21,50 - 54,98)	35 (41,2)	13 (15,4)	37 (43,4)
According to the group cause of the disease				
Gram (+) (n= 33)	17,75 ± 10,63 (13,98 – 21,52)	16 (48,5)	4 (12,1)	13 (39,4)
Gram (-) (n=44)	15,45 ± 9,48 (12,56 ± 18,33)	16 (36,3)	8 (18,2)	20 (45,5)
Fungi (n = 8)	19,97 ± 13,45 (8,72 – 31,22)	3 (37,5)	1 (12,5)	4 (50)
According to the cause of the disease				
S. aureus (n=24)	19,48 ± 11,22	13 (54,2)	2 (8,3)	9 (37,5)
K. pneumonia (n=14)	15,12 ± 32,46	6 (42,9)	2 (14,2)	6 (42,9)
Candida (n = 8)	19,97 ± 13,45 (8,73 ± 31,22)	3 (37,5)	1 (12,5)	4 (50)
E. coli (n=14)	17,17 ± 10,05	6 (42,9)	2 (14,2)	6 (42,9)
S. agalactiae (n=7)	11,75 ± 7,46	2 (28,5)	2 (28,5)	3 (43)
Khác (n=18)	17,42 ± 10,80	5 (27,8)	4 (22,2)	9 (50)

The mean white blood cell count in the blood was 16.78 ± 10.31 (10^9 cells/L). There were 41.2% newborns with increase WBC, 15.4% newborns decreased WBC.

Table 3.14. Peripheral blood platelet values (n=85)

Index	X ± SD (10^9 cells/L)	Increase (n, %)	Normal (n, %)
General	211,69± 204,45	42 (49,6)	43 (50,4)
According to the group cause of the disease			
Gram (-) (n=44)	161,84 ± 179,06	26 (59,1)	18 (40,9)
Gram (+) (n=33)	303,15 ± 224,00	10 (30,3)	23 (69,7)
Candida (n=8)	108,63 ± 89,77	6 (75)	2 (25)
According to the cause of the disease			
S. aureus (n=24)	359,63 ± 221,79	5 (20,8)	19 (79,2)
K. pneumonia (n=14)	146,50 ± 190,73	5 (35,7)	9 (64,3)
E. coli (n=14)	199,57 ± 179,24	6 (42,9)	8 (57,1)
S. agalactiae (n=7)	176,57 ± 170,48	3 (42,8)	4 (57,2)
Candida (n=8)	108,63±89,77	6 (75)	2 (25)
Others (n=18)	279,80 ± 190,20	17 (94,4)	1 (5,6)

The mean number of platelets in the blood was 211,69 ± 204,45 (10^9 cells/L). There were 49,6% newborns with platelets < $100x10^9$ cells/L. There were no newborns with thrombocytopenia.

Table 3.15. Concentration of CRP (n=85)

Index	**X ± SD** (mg/L)	**Increase** (n, %)	**Normal** (n,%)
General	84,2 ± 76,8	75 (88,3)	10 (11,7)
According to the group cause of the disease			
Gram (-) (n=44)	87,9 ± 80,4	38 (86,4)	6 (13,6)
Gram (+) (n =33)	88,6 ± 76,4	32 (96,9)	1 (3,1)
Fungi (n = 8)	45,4 ± 49,1	5 (62,5)	3 (37,5)
According to the cause of the disease			
S. aureus (n=24)	88,5 ± 67,2	23 (95,8)	1 (4,2)
K. pneumonia (n=14)	75,3 ± 53,6	13 (92,8)	1 (7,2)
E. coli (n=14)	107,9 ± 113,3	11 (78,6)	3 (21,4)
Candida (n = 8)	45,4 ± 49,1	5 (62,5)	3 (37,5)
S. agalactiae (n=7)	97,9 ±97,9	7 (100)	0
Others (n=18)	42,2 ±35,7	16 (88,9)	2 (11,1)

The average CRP concentration in the blood was 84.2 ± 76.8 mg/L, most of the patients had elevated CRP (88,3%).

Table 3.16. Assess coagulation status (n=80)

	X ± SD	**Decrease** (n,%)	**Normal** (n,%)	**Increase** (n,%)
Prothrombin (%)	65,5 ± 26,2	48 (60)	32 (40)	
APTT (giây)	47,5 ± 23,3		34 (42,5)	46 (57,5)
Fib (giây)	3,5 ± 1,5		40 (50)	40 (50)

There were 60% babies with decreased prothrombin, 57,2% and 50% of newborns increased APTT and Fib.

Quantification of immunity indicators

This is the first study in Vietnam on the values of immunological indices nCD64, mHLA-DR and SI in newbornss. We have quantified the indicators on 85 newborns with positive blood culture, 50 patients without infection, 175 patients with negative blood culture and recorded the following results:

Table 3.19: Values of nCD64, mHLA-DR, SI of newbornss with sepsis and no infection (n=135)

Index	**Sepsis (n=85)**	**Non-infection (n=50)**	**P value**
nCD64 (molecules/cell)	10167,1 ± 6136,9 (1198 -32965)	1900,9 ± 1589,1 (238 - 7569)	< 0,01
mHLA-DR (molecules/cell)	9898,4 ± 14173,9 (434 – 96881)	30476,8 ± 20205,1 (3052 -93049)	< 0,01
SI	274,6 ± 287,5 (18,7 - 1376,8)	7,9 ± 5,5 (1 – 22)	< 0,01

The nCD64 and SI values were higher and the mHLA-DR was significantly lower than the group without infection (p<0.01).

Table 3.20: Values of nCD64, mHLA-DR, SI of patients with positive blood culture sepsis and negative blood culture infection (n=257)

Index	**Positive blood culture (n=85)**	**Negative blood culture (n=172)**	**P value**
nCD64 (molecules/cell)	10167,1 ± 6136,9 (1198 -32965)	5985,1 ± 4916,3 (783 - 47953)	< 0,01
mHLA-DR (molecules/cell)	9898,4 ± 14173,9 (434 – 96881)	13897,1 ± 27223,2 (7 – 311904)	> 0,05
SI	274,6 ± 287,5 (18,7 - 1376,8)	(153,3 – 570,0) 3,5 - 7313	> 0,05

nCD64 of sepsis group with positive blood culture was significantly higher than that of neonatal infection group with negative blood culture, p < 0,01. There was no difference in mHLA – DR and SI values between the 2 groups, p > 0,05.

Table 3.22: Area under the ROC curve examines the value of laboratory indicators in the diagnosis of neonatal sepsis

Index	***Aera inder the curve (AUC)***	***P value***
WBC	0,48	0,60
PLT	0,34	0,00
CRP	0,74	0,00
nCD64	0,80	0,00
mHLA-DR	0,34	0,00
SI	0,80	0,00

SI and nCD64 had the highest diagnostic value (AUC = 0,8, p = 0,00);mHLA-DR has low diagnostic value (AUC=0,34, p=0,00)

3.2.Determination and antibiotic sensitivity of some common agents causing neonatal sepsis at the National Children's Hospital

Gram-negative bacteria accounted for the highest percentage 51,8%, Gram-positive bacteria accounted for 38,8%, fungi 9,4%.For early sepis, Gram-negative accounted for the highest rate of 77,3%.In the group of late bacterial infections, Gram-positive bacteria were the most common (69,7%), mainly *S. aureus (79,2%)*.The 8 newborns with fungal infections were all in the early-onset group, *S. aureus* was the most common cause (28,2%), *E.*

*coli*and *K. pneumonia* accounted for 16,5%, *GBS* accounted for 8,2%.

3.2.2. The susceptibility of pathogens to antibiotics

Table 3.31: Antibiotic resistance rate of bacteria (n=85)

Antibiotics	Sensitive		intermediary		Resistance	
	n	%	n	%	N	%
Ceftriaxon	16	61,5	0		10	38,5
Vancomycin	33	100	0		0	0
Ertapenem	13	81,3			3	18,7
Meronem	22	78,6			6	21,4
Meropenme	12	63,2			7	36,8
Imipenem	17	70,8			7	29,2
Tobramycin	12	63,2	1	5,2	6	31,6
Cefoxitin	10	47,6			11	52,4
Ciprofloxacin	33	73,3			12	26,7
Ceftazidim	11	44,0			14	56,0
Cefepime	7	70,0			3	30,0
Amikacin	25	65,8	4	10,5	9	23,7
Oxacilin	4	13,8			25	86,2
Ampicillin + Sulbactam	6	21,4			22	78,6
Benzylpenicillin	5	20,0			23	80,0
Piperacaclllin + Tazobactam	12	80,0			3	20,0
Aztreonam	12	85,7			2	14,3
Cefotaxim	3	20,0			12	80,0
Cefazolin	1	33,3			2	66,7
Cefoperazone	1	50,0			1	50,0
Fosmicin	4	66,7			2	33,3
Gentamycin	31	58,5	4	7,5	18	34,0
Moxiflocaxin	29	85,3			5	14,7
Levofloxacin	37	66,1	11	19,6	8	14,3
Casopofungin	8	100				
Fluconazol	8	100				
Micafungin	8	100				
Voriconazole	8	100				
Amphotericin B	8	100				

Antibiotics with high sensitivity are vancomycin (100%), moxiflocaxin (85.3%), ertapenem (81,3%), meronem (78,6%).Antibiotics with a high rate of resistance include cefotaxime (80,0%), benzylpenicillin (80,0%), ceftazidime (56%), cefoperazone (50%).Casopofungin, micafungin, voriconazole, amphotericin B are also sensitive to *Candida*.

Table 3.32: Rate of antibiotic sensitivity of bacteria (n=85)

Antibiotics	*K.pneumonia*	*E. coli*	*S. marcescens*	*P.aeruginosa*	*S. agalactiae*	*S. aureus*	*C. albicans*
Ceftriaxon	4/8	6/9	3/4				
Vancomycin					7/7	24/24	
Ertapenem		4/9		2/2			
Meronem	11/12	6/9		½			
Meropenme	¾	3/8		2/2		2/24	
Imipenem	6/8	8/11					
Clindamycin					2/7	1/16	
Tobramycin		4/8	3/4				
Cefoxitin	3/8	5/9	1/4				
Ciprofloxacin	5/8	3/7	1/2	2/2		17/24	
Ceftazidim	5/11	4/6	3/4				
Cefepime	2/12	4/10					
Amikacin	6/8	12/13	3/4				
Oxacilin					4/7		
Ampiillin+ Sulbactam		2/11			2/7	1/24	
Benzylpenicllin					5/7		
Piperacaclllin +Tazobactam	5/9	3/11	1/1			1/24	
Aztreonam	5/9	4/9	3/4				
Cefotaxim							
Cefazolin							
Fosmicin			1/3				
Gentamycin	3/8	7/13	3/4	½		15/18	
Moxiflocaxin		2/10	1/2	½	5/7	15/24	
Levofloxacin	4/8	4/8	3/4	2/2	6/7	20/24	
Casopofungin							8/8
Fluconazol							8/8
Micafungin							8/8
Voriconazole							8/8
Fluorocytosine							8/8
Amphotericin B							8/8

S. aureus is 100% sensitive to vancomycin and levofluxaxin; *E. coli* is also sensitive to amikacin (12/13), imipemen (8/11), meropenem (6/9). All antifungal agents are still susceptible to *Candida.*

3.3. Outcomes of full-term neonatal sepsis at the National Childern's Hospital.

3.3.1. Outcomes of therapeutic interventions

Table 3.33. Patient's condition at hospital discharge (n = 85)

Outcomes		Number	%
Alive		59	69,4
	No sequelae	58	68,2
	Sequelae	1	1,2
Death at the hospital		19	22,4
	In 24 hours	2	2,4
	After 24 hours	17	20,0
Withdraw of treatment		7	8,2
Total		85	100

There were 59 patients alive, accounting for 69,4%, of which 1 child showed neurological sequelae at the time of discharge (hypertonia). There were 26 dead or withdraw of treatment, accounting for 30,6%, of which 19 died (22,4%), and 7 seriously ill patientswithdrawed (8,2%).

Mortality was higher in the early-onset group (36,5%) than in the late-onset group (21,1%). The mortality rate in the group of newbornss with fungal infections was 50%, with Gram-negative bacteria was 40.9%, and with Gram-positive infections was 12,1%. The mean duration of treatment was 23,1 ± 19,8 days, the survival group was 27,4 ± 19,8 days, the death group returned 14,1 ± 16,7 days, the maximum duration of antibiotic use was 66 days. Longest mechanical ventilation was 40 days, longest HFO support was 8 days. There were no newborns on dialysis and ECMO. We have 53/85 mechanical ventilation, 57/85 central catheterization. 47,2% of patients with mechanical ventilation died, 43,8% of patients with intravenous catheters died. The difference in death/return between the two groups with and without surgical intervention was statistically significant with $p < 0,01$.

3.3.2. Evaluation of some factors related to treatment outcome

During the study, we recorded 59 patients in the survival group and 26 patients in the death group. We found that front-line mechanical ventilation is a factor that increases the risk of death 3,2 times (1,6-12,9) times ($p<0,05$). Mechanical ventilation at the National Newborns's Hospital increases the risk of death 27,7 times (3,5-217,8), $p < 0.01$. Catheter placement increased the risk of death 21,1 times (2,7-166,1), $p < 0,01$. Septic shock increased the risk of death by 5,1 times (1,9 – 14,0), $p < 0,05$, WBC < $4x10^9$/L increased the risk of death 4,8 (1,4 - 16,5) times, ($p < 0,05$), PLT<$100x10^9$/L increases the risk of death 4,2 (1,5 -11,7) times ($p < 0.05$).

Chapter 4
DISCUSSION

4.1. Clinical and laboratory characteristics of sepsis in term neonates.

Research results show that boys (54,1%) are higher than girls (45,9%), but the difference is not statistically significant. The results are comparable to some national and international studies.

Most of the newborns admitted to the National Children's Hospital were treated at previous levels (91,8%) and had many interventions. Currently, many modern technical procedures from the National Children's Hospital have been transferred to the lower level. Invasive procedures such as endotracheal intubation, central line are the main risks of increasing the rate of sepsis especially late onset neonnatal sepsis, acquired bacteria are usually hospital-acquired bacteria with a high rate of antibiotic resistance. Therefore, the intervention of procedures should be strictly indicated, performed with the correct technique in a safe environment to minimize the risk of infection for the child.

4.1.9. Clinical manifestations of sepsis in term neonates

Time of onset of symptoms of infection in newborns: The rate of early-onset sepsis in our study was 61,2% higher than the late-onset group at 38,2%, equivalent to the results at the Obstetrics and Gynecology Hospital. Center. A report in Nigeria also showed that the rate of early-onset sepsis (77,8%) was 3 times higher than the rate of late-onset sepsis(22,2%). However, at present, in the world, the trend of early neonatal sepsis is decreasing and the rate of late neonatal sepsis is increasing. Agnes van den Hoogen tracked the data from 1978-2006, the rate of early sepsis decreased from 52,1% to 28,1%, in contrast, the rate of late sepsisincreased from 11,4% to 13,9%. The reason may be that now the management of pregnancy is better, the mother is prevented from GBS to avoid infecting the baby, and the mother's infections are better managed. However, the pathologies of newborns treated in the neonatal intensive care unit increased, so the rate of late-stage nosocomial infections increased.

Characteristics of newborn's temperature: The rate of newborns with fever accounted for 51,8%, equivalent to the results of Abebe Sorsa's study in Ethiopia with the rate of 475% of full-term infants with sepsis but higher than the rate of 23,9% in Joshua Davis's study. The rate of newborns with fever in our study was also much higher than that of patients with fungal infections in Thai Bang Giang's study (4,1%).

Respiratory symptoms in newborns: Among respiratory symptoms, a decrease in spO2 was the most common sign (75,3%) equivalent to the study of Tran Dieu Linh (73,3%) but higher than that of Abebe Sorsa (34%).

Circulatory symptoms in newborns: Tachycardia was the most common manifestation of 51,8%, especially 29,4% of newborns with septic shock, equivalent to the results of Barbara J Stoll but lower than Eric Giannoni (16,8%). The prolonged rate of shock and refill showed that many newborns were hospitalized in severe condition.

Digestive symptoms of newborns: Poor feeding was the most common digestive symptom 92,9%, equivalent to the study by Tran Dieu Linh and Thai Bang Giang.

Neurological symptoms of newborns: 29,4% of newborns lethargic, 11,8% of newborns were excited. There are 2 patients with seizures, 2 patients with hypertonia, 1 patient with hypotonia. However, some newborns admitted to the hospital were sedated, so neurological symptoms were not accurately assessed.

Skin symptoms of newborns: The rate of scleroderma in our study was similar to that of Bui Man Nguyen in the neonatal study of sepsis at Hai Phong Newborns's Hospital (21,4%) which is a severe manifestation of sepsis.

4.1.10. Paraclinical characteristics of full-term neonatal sepsis

Peripheral blood Hct concentration: 72,9% of anemic newborns, lower than Na Cai (84,9%) but similar to the group of newborns with blood fungal infections of Thai Bang Giang (32,4%).

Peripheral blood leukocyte values: The percentage of newborns with elevated WBC and decreased WBC in our study were lower than in Tran Dieu Linh's study in the cesarean section group (55,5% and 22,2%). Newman and Hornik C.P 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 WBC has diagnostic value in early-onset sepsis rather than late-onset.

The value of platelets in the peripheral blood: Our rate of thrombocytopenia was higher than that of Isabelle M. C. Ree's study with the proportion of newborns with PLT< $150x10^9$/L accounted for 49%, TC decreased < $100x10^9$/L accounted for 39%. The rate of lowering PLT< $150x10^9$/L in neonatal sepsis due to Gram-negative bacteria is 69%, due to Gram bacteria is 47%. Some hypothesize that in the setting of sepsis, endothelial injury triggers reticuloendothelial platelet rejection.

Value of CRP: Most had CRP increase above 15mg/L (88,3%). Delanghe J.R suggested that CRP has low sensitivity to detect early-onset sepsis due to the physiological increase in CRP in 3 days postpartum.

Coagulation characteristics of newborns: We have 60% of patients with reduced prothrombin equivalent to Vo Van Hoi's results on neonatal

sepsisgroup at Da Nang Obstetrics and Gynecology Hospital. Coagulopathy is a serious complication in neonatal sepsis.

Quantification of immunological indices: This is our first study on the quantification of nCD64, mHLA-DR and SI indices.

Quantitative nCD64: Our group of sepsis patients had an average of nCD64 5,3 times higher than the mean value of the non-infectious group and 2 times higher than the group of newborns with sepsis with negative blood cultures.

nCD64 is a marker that has been evaluated to be valuable in the diagnosis of sepsis with high specificity and sensitivity. However, the cut-off point varies depending on each study, research object, method. Research by Pham Thi Ngoc Thao selected the cut-off point of nCD64 = 1311 molecules/cell to assess the sepis status of adult patients. Hugh Simon Lam studied on a group of premature neonates with necrotizing enterocolitis and showed the cut-off point nCD64 = 23777 molecules/cell. Our study uses quatibrite to evaluate, so it has a higher accuracy than measured by mean fluorescence density (MFI).

The mHAL-DR positive blood culture group had a value equivalent to 32,4% of the value of the healthy group (30476,8 ± 20205,1 molecules/cell). Talita Freitas Manzoli showed that <30% reduction in mHLA-DR compared with controls was a predictor of mortality in the first week of hospital admission. Most of our patients are transferred from lower-level hospitals when treatment has failed, so most of them are in serious and very serious condition.

Quantification of SI: In our group of infants with positive blood cultures, SI had an average value of 274,6 ± 287,5 (18,7 – 1376,8), much higher than the value of infants without infection (SI = 7,9). The bacteremia index SI has been described as a prognostic biomarker of sepsis. Bibiana Quirant Sanchez showed that SI increased significantly in patients with infection compared with patients without infection ($p < 0,001$).

When investigating the diagnostic value of immunological indicators in diagnosing sepsis in full-term neonates, we found that nCD64 and SI are the indexes with the highest value with the area under the curve 0,80, $p < 0,001$. While commonly used indicators to diagnose infections such as CRP, platelets, and white blood cells have much lower values (AUC < 0,75).

Our cut-off score nCD64 = 5004 molecules/cell was higher than Pham Thi Ngoc Thao's study but lower than Hugh Simon Lamdo because the subject of Hugh Simon Lamdo's study was a group of full-term infants. Pham Thi Ngoc Thao also showed that the SI index > 39,69 has higher sensitivity and specificity than leukocytes, CRP, and procalcitonin in diagnosing sepsis in adults with trauma. Our SI value was lower than the author's because the subjects in our study were infants.

4.2. Objective 2: Determine the causative agents of neonatal sepsis and antibiotic sensitivity.

4.2.1. Classification of microorganisms according to the nature of Gram staining

Gram-negative bacteria accounted for the highest percentage (51,8%), Gram-positive bacteria accounted for 38,8%, fungi 9,4%. The microbial cause of early sepsis with the highest rate was Gram-negative (n=77,2%), mainly *E. coli* and *K. pneumonia*. In the group of late bacterial infections, Gram-positive bacteria accounted for the highest rate (69,7%), mainly *S. aureus* (n = 19), Gram-negative bacteria only accounted for 22,8%. All infants with blood fungal infections showed symptoms very early. Our results are equivalent to Gowda H, Michael Cohen-Wolkowiez, Poonam Sharma. Our rate of *S. aureus* is also similar to (76,5%) and Ogundare E (83,3%).

4.2.3. The rate of antibiotic resistance of bacteria

Vancomycin is 100% sensitive to the bacteria analyzed. Antibiotics with a high sensitivity rate are moxiflocaxin (85,3%), ertapenem (81,3%), meronem (78,6%). Our results are equivalent to Do Thien Hai researched in 2016, Ha Duc Dung researched at the National Hospital of Obstetrics and Gynecology in 2019, Sharma P.

Assessing the susceptibility of antibiotics to pathogens, we found that *E. coli* was still sensitive to amikacin (12/13), gentamycin (7/13), imipemen (6/9), meropenem (8/11); *K. pneumonia* is moderately sensitive to many antibiotics including levofloxacin (4/8), imipenem (6/8), amikacin (8/14). *P. seudomonas*was also sensitive to meronem, imipenem. *S. aureus* was also sensitive to vancomycin, ciprofloxacin, levofloxacin, moxiflocaxin, gentamycin, especially 100% sensitive to vancomycin. *GBS*was also sensitive to vancomycin, levofloxacin and moxifloxacin. *Candida* is sensitive to all currently used antifungal agents. Around the world, the problem of antibiotic resistance in the treatment of neonatal infections varies from type of bacteria and from country to country. In rural India, *S. aureus* is still sensitive to 2nd and 3rd generation cephalosporins and vancomycin. However, Gram-negative bacteria are almost exclusively sensitive to amikacin and quinolones. Abdelhamid S. M, a study in Egypt in 2017 reported that all Gram-positive bacteria were susceptible to vancomycin and tigecycline. Most Gram-negative bacteria were resistant to cephalosporins but are sensitive to levofloxacin. Thus, Gram-positive bacteria were resistant to penicillin or oxacillin but still had a high rate of sensitivity to vancomycin. Meanwhile, the group was resistant to cephalosporin antibiotics with a high rate, only sensitive to quinolones and imipenems. Although quinolones are proven to be increasingly

safe, the treatment of this group of antibiotics in susceptible subjects such as neonates still requires consideration and monitoring for side effects.

4.3. Outcomes of neonatal sepsis at term and some related factors.

4.3.1. Overall outcomes

The results of our study showed that 69,4% of the infants lived, of which 1 had neurological sequelae (generalized hypertonia), 19 infants died (22,4%) including: including 2 infants who died within the first 24 hours (2,4%), and 7 seriously ill infants (8,2%). Our rate of child deaths and withdraw of treatment accounted for 30,6%. The National Children's Hospital is the last line to receive serious patients who have failed treatment from the provincial and district levels, so the condition of the patients on admission was very serious. In which, many patients were resistant to antibiotics or were in septic shock or multi-organ failure. Therefore, although many modern equipments have been equipped and many high techniques have been deployed, the infant mortality rate is still very high.

Regarding the time of onset of infection related to treatment results, in our study, the mortality rate due to early onset sepsis was higher (36,5%), the mortality rate of late onset neonatal sepsis group was lower (21,1%). Currently, the world trend is that the infant mortality rate in the early stage tends to decrease compared to the late infection group because there have been many advances in maternal and child care.

Assessing the relationship between pathogens and treatment results, we found that the mortality rate due to Gram-negative bacteria and fungi was very high, 40,9% and 50%, respectively. Mortality rate in the sepsis group due to Gram-positive bacteria was low, 12.1%. In most studies, mortality was higher in Gram-negative bacteria than Gram-positive bacteria.

4.3.2. Average day of treatment

In our study, the average treatment day was 23,1±19,8 (0-106) days. The mean treatment day of the surviving group was 27,4 ± 19,8 days, the death/withdrawed of treatment was 14,1 ± 1617 days. Our treatment time was longer than Sara Erol's study on *P. seudomonas pneumonia* (15 days) but shorter than Thai Bang Giang's study on newborn fungal infections (48,2 days) due to the difference of research subjects.

4.3.3. Duration of treatment according to the cause in the group of alive infants

Surveying the duration of treatment in the live neonate group, we found that infants with fungal infections had the longest treatment time until they were discharged from hospital with 66,5 ± 14,6 days. Our results were higher than the group of newborns with fungal infection in Thai Bang Giang's study

(50,3 ± 17,7 days). Claudia Reinheimer's study on pediatric sepsis infected with *GBS*, the treatment time was from 2–156 days, the average duration of treatment was 8 days. Thus, each different cause of disease has different treatment regimens, so the treatment time is also different.

4.3.4. Some interventions in the treatment of full-term neonatal sepsis

Invasive interventions

In our study, the rate of infants on invasive mechanical ventilation accounted for 62.4%, the mortality rate in the mechanical ventilation group was 47,2%; 67,1% of infants had central venous catheters, of which 43.8% died. The higher rate of infants requiring mechanical ventilation, catheterization and mortality in our group of infants with surgical intervention shows that the patient is seriously ill at the National Children's Hospital.

Antibiotics used in the treatment of bacterial infections.

Most infants had to combine at least 2 antibiotics for treatment, in which the mortality rate in the group using 7 antibiotics and 8 antibiotics was 50% and 40%, respectively. This shows that choosing the right antibiotic in the beginning is very important to reduce the risk of antibiotic resistance and side effects, and increase the effectiveness of treatment.

Blood and blood products to be transfused with the patient

We found that the percentage of infants requiring fresh plasma transfusion due to decreased prothombin and fibirinogen died at 66,7%, much higher than many groups of infants who had to receive platelet and red blood cell transfusions. Our results are similar to the study of Bui Man Nguyen at Hai Phong Infants's Hospital. The author showed that the group of neonates who died due to sepsis had significantly decreased prothombin ratio and mean fibrinogen concentration compared with the group of infants who survived ($p < 0,001$).

4.3.5. Risk factors related to treatment outcome

Front-line mechanical ventilation, mechanical ventilation, central catheterization at the National Children's Hospital are factors that increase the risk of death 4,5 times; 27,7 and 21,1 times.

Patients requiring invasive surgical intervention for mechanical ventilation and catheterization were serious patients with high mortality prognosis. In addition, infants who needed these procedures are at higher risk of nosocomial infections.

White blood cell count < $4x10^9$/L was a factor that increased the risk of death 4,8 times

Jan M. Kruse study of adult septicemia showed that the group of patients with decreased neutrophils (<$1x10^9$/L) lasting > 24 hours had a risk of death 7,95 times higher than the group without leukopenia.

Platelets <100x10^9/L increased the risk of death 4,2 times

Research by Vo Van Hoi shows that infants with one of the manifestations of disseminated intravascular coagulation, platelets ≤ 100x10^9/L, prothrombin ratio < 50% have a 10-15 times higher risk of death compared with the group of infants without these manifestations (p < 0,01). Bui Man Nguyen also found that a decrease in platelet count < 100x10^9/l in neonates with sepsis was a factor that increases the risk of death 13,3 times compared with infants with a normal platelet count.

Septic shock is a factor that increased the risk of death by 5,1 times (p < 0,05).

The state of shock when not improved in time leads to multi-organ failure very quickly and seriously. Research by Nguyen Thi Kim Nhi at the Department of Neonatology at Children's Hospital 1 showed that septic shock increased the mortality rate by 3,3 times (1,1 – 11,2), respectively.

CONCLUSION

A study from December 1, 2019 to April 30, 2021 on 85 infants who were eligible for the study, hospitalized for treatment at the Neonatal Center of the National Children's Hospital, has the following conclusions:

1. Clinical and subclinical characteristics of sepsis in term neonatesat the National Children's Hospital.

- Clinical features: Full-term neonatal sepsis was found in boys and girls with similar rates (54.1% and 45,9%), Common clinical symptoms are: poor feeding (89,4%), respiratory failure (75.3%), fever (51,8%), tachycardia (51,8%), shock (29,4%).

- Paraclinical characteristics: Anemic patients accounted for a high rate (72,9%), there were 49,6% children with low platelets. Most children had elevated CRP (88,3%). The mean value of nCD64 was 10167.1 ± 6136.9 molecules/cell, mHLA-DR was 9898,4 ± 14173,9 molecules/cell, SI was 274,6 ± 287,5. SI and nCD64 have high values in the diagnosis of neonatal NKH at term (area under the curve AUC = 0,8, p < 0,01).

2. Determination and antibiotic sensitivity of some common agents causing neonatal sepsis.

Pathogens: Gram-negative bacteria accounted for the highest proportion 51,8%, Gram-positive bacteria accounted for 38,8%, fungi accounted for 9.4%. *S. aureus* is the common cause of disease (28.2%), E. *coli* and *K. pneumonia* account for a high proportion (16,5%).

Rates of susceptibility and antibiotic resistance of pathogenic bacteria: The antibiotics with high sensitivity are vancomycin (100%), moxiflocaxin

(85.3%), ertapenem (81.3%), meronem (78.6%). Antibiotics with a high rate of resistance include cefotaxime (80.0%), benzylpenicillin (80.0%), ceftazidime (56%), cefoperazone (50%). S. aureus is 100% sensitive to vancomycin and levofluxaxin; E. coli is also sensitive to amikacin, imipemen, and meropenem. *Candida* is also sensitive to the antifungal drugs being used.

3. Evaluation of the results of full-term neonatal sepsis treatment at the National Children's Hospital.

Treatment results: Survival rate 69,4%, neurological sequelae 1,1% (generalized hypertonia), mortality and morbidity about 30,6%. Average treatment day is 23,1 ±19,8 days. The early infection group had a higher mortality rate (36,5%) than the late infection group (21,1%). Mortality rate in children with fungal infection was 50%, Gram-negative bacteria was 38.2%, Gram-positive was 12,1%. *E. coli* was the most deadly bacteria.

Factors related to treatment outcome: Factors that increase the risk of neonatal mortality with sepsis include front-line mechanical ventilation (OR = 3,2, (1,6 - 12,9)), $p < 0,05$), mechanical ventilation (OR = 27,7 (3,5-217,8), $p < 0.01$), catheterization (OR = 21,1 (2,7-166,1), $p < 0,01$), septic shock (OR = 5,1 (1,9 - 14.0)), $p < 0.05$), white blood cell < $4x10^9$ cells/L (OR = 4,8 (1,4 – 16,5)), $p < 0,05$), platelets < $100x10^9$ cells/L (OR = 4,2 (1,5 -11,7), $p < 0,05$).

RECOMMENDATION

For early and accurate diagnosis of neonatal sepsis, which requires a combination of indicators, the possibility of including nCD64, mHLA-DR and SI in the test kit in atypical or interventional cases should be considered. treatment from the front line.

Based on the pathogenic bacteria model, it is possible to develop a unified guideline on the diagnosis and treatment of neonatal sepsis for all health facilities, especially the initial use of antibiotics.

To prevent neonatal sepsis, it is necessary to increase training in medical facilities on treatment measures, ensure sterility of invasive procedures, and implement good nosocomial infection control to reduce the risk of infection. It is necessary to strengthen propaganda on hygiene and infant feeding to reduce the risk of neonatal sepsis from the community.