

CLINICAL AND MICROBIOLOGICAL FEATURES OF EARLY-ONSET NEONATAL SEPSIS IN PRETERM INFANTS

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Abstract

Early-onset neonatal sepsis (EONS) remains the leading cause of morbidity and mortality, especially among premature infants. Conducting high-quality epidemiological monitoring is an important condition for effective tactics treatment neonatal infections and improving the quality of medical care for this category of newborn.

The aim. Determination of the value of microbiological triggers in the blood in various clinical options for EONS in preterm infants.

Materials and methods. Clinical and microbiological data on 50 prematurely born newborns with EONS were selected. The analysis of the frequency of detected bacteremia, the distribution of pathogenic microorganisms and the clinical characteristics of neonatal sepsis.

Results. In the study, sources of infection were detected in 94 % of cases. Positive blood cultures were obtained in 17 (34 %) newborns with EONS. 61.5 % of all cases of bacteremia were caused by coagulase-negative staphylococcus (CoNS). Gram-negative pathogens were detected in 23.5 % of positive blood cultures, representatives of this group were *Escherichia coli* and *Klebsiella pneumoniae*. The overall mortality rate from EONS was 30 %.

Conclusions. The incidence of sepsis confirmed by a positive blood culture was 34 %. The most common cause of EONS is CoNS, low incidence of group B Streptococcus sepsis has been established. The most frequent septicopymic sources of infection were the lungs, which is expressed in the high incidence (94 %) of X-ray pneumonia in the structure of the EONS.

Keywords: early-onset neonatal sepsis, epidemiology, preterm infants.

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1. Introduction

Despite measures to improve the quality of care for newborns, neonatal sepsis (NS) is the cause of significant morbidity and mortality [1, 2]. Compared to full-term infants, NS is more common in premature babies and is associated with a higher mortality rate and the further development of long-term adverse effects, including severe disabling lesions of the central nervous system [3, 4].

Depending on the time of implementation of the clinical manifestations, it is customary to distinguish between early neonatal sepsis (EONS) and late onset neonatal sepsis (LONS). EONS develops in the first 72 hours after birth, usually due to transplacental or ascending infection [5].

The frequency of culture-proven EONS in the USA is 0.77 per 1000 live births, in Norway 0.54 per 1000 live births [6, 7]. The frequency of EONS in Australia is 0.69 per 1000 newborns, and in Switzerland – 0.28 per 1000 live births [8, 9].

In more than 85 % of infants, EONS symptoms appear in the first 24 hours of life, in 5 % within 24–48 hours after birth, in a small number of newborns, the disease is diagnosed in the interval from 48 to 72 hours of life [10].

The non-specificity of clinical symptoms and the insufficient diagnostic value of existing laboratory tests lead to defects in the registry and monitoring of this disease, the inability to conduct an unambiguous assessment of the existing epidemiological and microbiological

situation in various health systems and the subsequent effective implementation of preventive measures [11].

Sterile bacterial culture is the “gold” standard for the diagnosis of NS, however, blood cultures have certain limitations. It should be noted that the inability to isolate the microbial pathogen in the blood of a newborn child does not exclude the diagnosis of sepsis [12].

Pathogens that cause EONS and their susceptibility to antibiotics have significant differences in different countries [13]. Therefore, conducting epidemiological monitoring of neonatal infections is an important condition for ensuring timely, effective therapeutic policies within a single intensive care unit, hospital, and public health system.

The aim of the study. Determination of the value of microbiological triggers in the blood in various clinical options for early neonatal sepsis in premature infants.

2. Materials and methods

The study was conducted from 2016 to 2019 on the base of Kharkiv city perinatal center. An analysis of 50 cases of EONS in prematurely born infants at 24 to 36 weeks of gestation was performed. A detailed description of the patients is given in **Table 1**.

Table 1

Patient Characterization

Characteristic	n	%
Gender		
Male	27	54
Female	23	46
Gestational age (weeks)		
<28	24	48
28-32	14	28
33-36	12	24
Birth weight (grams)		
≤999	20	40
1000–1499	13	26
1500–1999	9	18
≥2000	8	16

The diagnosis of EONS was made according to the standards of management of newborns with suspected early neonatal guidance for management of Early Onset Sepsis NICE (National Institute of Clinical Excellence) infection. In addition to assessing the clinical picture of the disease, laboratory studies were carried out, including counting the number of leukocytes (white blood cells >15 or $<5 \cdot 10^9/l$), the ratio of immature to the total number of neutrophils (ratio I:T >0.3), the concentration of C-reactive protein (diagnostic value in venous blood >10 mg/l), procalcitonin (diagnostic value in venous blood >2 ng/ml).

Venous blood for cultures and laboratory tests (mainly WBC, C-reactive protein, and procalcitonin) was obtained at the onset of clinical symptoms of infection before antibiotic therapy. Other studies have been clinically indicated and included chest or abdominal radiography, microscopy and culture of cerebrospinal fluid, and tracheal aspiration culture. The protocol of the study was in accordance with the Council of Europe Convention on Human Rights and Biomedicine, the Helsinki Declaration of the World.

Statistical analysis was performed using the software package Microsoft Office Excel and Statistica. Nominal data were described with absolute values and percentages. According to the expected and observed frequency Fisher's exact test was used for contingency tables. Results associated with p-values <0.05 were considered statistically significant. Data were analyzed using phi correlation coefficient.

3. Results

Among the newborns examined, 38 children (76 %) were born <32 weeks of gestation, which of 20 (40 %) were born with extremely low body weight.

Source of infection were identified in 94 % of cases (**Table 2**). In most cases, the septicopyemic source of infection were lungs with an X-ray picture of pneumonia. In 3 children (6 %), the disease proceeded against an isolated *septicemia* without identifying a *septicopyemia* focus.

Table 2

Clinical forms of early onset neonatal sepsis in premature babies

Clinical course	n	(%)
<i>Septicemia</i>	3	6
<i>Septicemia</i> + Pneumonia	13	26
<i>Septicemia</i> + Meningoencephalitis + Pneumonia	1	2
Pneumonia*	13	26
Meningoencephalitis + Pneumonia	5	10
Pneumonia + NEC	8	16
Meningoencephalitis + Pneumonia + UTI	1	2
Pneumonia + UTI	4	8
Pneumonia + Omphalitis	2	4
Total	50	100

Note: * – pneumonia in newborns with clinical signs of sepsis with laboratory data of a systemic inflammatory response syndrome and multiple organ failure and/or shock, NEC – necrotizing enterocolitis, UTI – urinary tract infection

In the study, positive blood cultures were obtained in 17 (34 %) newborns with EONS. The main microbial agents were representatives of gram-positive cocci group.

Coagulase-negative staphylococcus (CoNS) was the most common pathogen, it accounted for 61.5 % of all cases of bacteremia.

Gram-negative pathogens were detected in 23.5 % of positive blood cultures, representatives of this group were *Escherichia coli* and *Klebsiella pneumoniae*. It should be noted that not a single isolate of fungal flora was found.

The structures of bacterial pathogens isolated in the blood are presented in detail in **Table 3**.

The mortality rate from EONS was 30 %. In the group of deceased newborns, severe hypoxic-hemorrhagic lesions of the central nervous system, the development of septic shock and multiple organ failure was observed (**Table 4**). The phi-square revealed a significant relationship between IVH 3 stage, septic shock, MODS and outcome of sepsis. Necrotizing enterocolitis (NEC), meningoencephalitis, urinary tract infection did not significantly affect the outcome of sepsis. This was also confirmed by the presence of a significant relationship in the interpretation of the Phi coefficient.

In children with positive blood cultures (n=17), 4 deaths were noted, which in 100 % of cases were due to gram-positive pathogens.

Table 3

Characterization of microbial pathogens of early neonatal sepsis in premature infants with positive blood culture

Pathogen	n	(%)
Gram-positive bacteria	13	76.5
Staphylococcus coagulase negative	8	47
<i>Listeria monocytogenes</i>	2	11.8
Group B Streptococcus	1	5.8
<i>Staphylococcus aureus</i>	2	11.8
Gram-negative bacteria	4	23.5
<i>Escherichia coli</i>	2	11.8
<i>Klebsiella pneumoniae</i>	2	11.8
Total amount	17	100

Table 4

EONS mortality predictors in premature babies

	Non- survival n=15	Survival n=35	Fisher's exact test	p	φ	Interpretation of the Phi coefficient
NEC	3	5	0.68255	>0,05	0.071	negligible positive relationship
IVH 3 stage	8	2	0.00039	<0,05	0.546	substantial positive relationship
Meningoencephalitis	3	4	0.41499	>0,05	0.113	low positive relationship
UTI	3	2	0.15174	>0,05	0.218	low positive relationship
Septic shock	7	2	0.00162	<0,05	0.488	moderate positive relationship
MODS	11	4	0.00003	<0,05	0.619	substantial positive relationship

Note: NEC – necrotizing enterocolitis, IVH – intraventricular hemorrhage, UTI – urinary tract infection, MODS – multiple organ failure syndrome, p – confidence level, φ – Phi coefficient

4. Discussion

Despite the actively ongoing search for new markers, blood culture is still recognized as the gold standard for the diagnosis of NS [14]. In our study, the incidence of positive blood culture in preterm infants with EONS was 34 %. The low level of bacteremia, as well as the insufficient volume taken for blood tests, especially in children with extremely low body weight, may be one of the explanations for a large number of cases of culture-negative sepsis. In addition, antibiotic treatment in the mother before or during childbirth may in some cases mask the detection of bacteremia in the newborn [15]. In cases where the blood cultures and other sterile cultures are negative, but the child shows signs that correspond to the implementation of the infectious process, they can be considered “clinical” sepsis [16].

Most publications on neonatal sepsis management from high-income countries include only culturally confirmed cases. A large number of newborns who received antibiotics for the treatment of sepsis with a negative result of seeding in epidemiological studies are largely ignored.

Reliable epidemiological data on culture-negative sepsis are limited [17]. Moreover, according to recent studies, it is known that the number of children receiving systemic antibiotic therapy in culture-negative sepsis exceeds the number of children receiving therapy with bacteriologically-confirmed sepsis.

The ratio of culture-confirmed and culture-negative cases of sepsis in Canada is 1:7, and in Norway the indicator reaches 1:16 [18, 19]. In the SCOUT study, researchers evaluated antibiotic intake for various conditions in 2,500 full-term and premature infants. Culture-confirmed infection and NEC accounted for only 6.9 % of antibiotic use [20]. At the same time, it was proved that prolonged antimicrobial therapy in children with negative blood cultures, without proven infection, increases the risk of mortality, bronchopulmonary dysplasia, NEC, retinopathy and damage to the white matter in the periventricular region, and also leads to the appearance of multi-resistant strains of microorganisms [21, 22]. On the other hand, delayed antibiotic therapy in truly infected newborns can lead to increased mortality and morbidity [23]. Thus, culture-negative NS is at the crossroads between effective sepsis treatment programs and antimicrobial programs.

In the study, the structure of pathogens was dominated by representatives of gram-positive bacteria, mainly CoNS (47 %). The study of the world microbiological landscape demonstrates a significant heterogeneity of the distribution of pathogens in the structure of the EONS.

So in the British and French studies, the dominant etiological factor in the development of EONS is GBS (43 % and 58.5 %, respectively) [24, 25]. In a Swedish study, EONS was triggered by group B Streptococcus at a significantly lower percentage (20 %), with CoNS accounting for 30 % [26]. The situation was different in South Korea and Denmark, where the main causative agent of EONS was *S. aureus* (48 % and 36 %) [27, 28]. Mexico and Turkey dominated CoNS with a prevalence of 55.5 % and 60.9 %, respectively, which is consistent with our research [29, 30].

Gram-negative bacteria in our study accounted for 23.5 %, this segment was represented by *E. Coli*, *K. Pneumonia*. As for *E. Coli*, in Israel this pathogen accounts for 20 % of cases of EONS, and the problem of infections of the early neonatal period caused by *Klebsiella pneumoniae* is relevant in Poland [31, 32].

In 30 % of cases, NS was fatal. The key risk factors for this outcome are known to be low gestational age and low birth weight [33]. Moreover, our data are consistent with studies emphasizing that multiple organ failure and septic shock are the most significant predictors of death in NS [34].

Study limitations. There were some limitations in this study. The study was conducted in a single center. Our observations may be less applicable to different institutions when compared with multicenter, prospective studies. Furthermore, there were sample size limitations. This could affect the limitation of microbiological characteristics.

A plan for further research includes the study of the diagnostic significance of modern markers of sepsis in preterm infants.

5. Conclusions

1. In our study, the incidence of early neonatal sepsis confirmed by a positive blood culture was 34 %.
2. The most common cause of EONS in premature babies is CoNS (47 %), and a low incidence of sepsis of group B Streptococcus (5.8 %) has been established.
3. Among the clinical forms of early NS, the most frequent septicopyemic source of infection were the lungs, which is expressed in the high incidence (94 %) of X-ray pneumonia in the structure of EONS.

Conflict of interest

The authors declare there is no conflict of interest.

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