Original Research Article: full paper

(2018), «EUREKA: Health Sciences»
Number 5

# DIAGNOSTIC VALUE PARAMETERS OF ACUTE PHASE REACTANCES OF INFECTIOUS-INFLAMMATORY PROCESS IN DIAGNOSTICS OF EARLY NEONATAL SEPSIS

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**Abstract**

An advanced progress of clinical neonatology in recent years has enabled to achieve considerable success in newborn management with due respect to both medical treatment and general care, especially in the group of neonates with low body weight at birth. At the same time, neonatal sepsis in the early period still predetermine sickness and mortality of newborns.

**Material and methods**. Clinical-paraclinical indices with detection of diagnostic value of C-reactive protein and interleukins-6 and 8 were evaluated in 100 neonates with available susceptibility factors to early neonatal infection from mother's side and clinical signs of organ dysfunction in neonates with precautions of generalized infectious-inflammatory process at the end of their first day of life.

**Results**. The data obtained substantiate that low concentrations of IL-6 and IL-8 prevail, and therefore the mentioned mediators hardly can be used to verify early neonatal infection. In the majority of children C-reactive protein elevated the concentration of 10.0 mg/L which is traditionally considered to be a discriminant as to the verification of an infectious process in newborns.

**Conclusions**. None of the clinical signs associated with infectious-inflammatory process in newborns in the first two days of their life enabled to verify reliably availability of systemic bacterial infection.

**Keywords**: neonatal sepsis, C-reactive protein, interleukin-6 and 8, parameters of diagnostic value.

**DOI: 10.21303/2504-5679.2018.00728**



## 1. Introduction

An advanced progress of clinical neonatology in recent years has enabled to achieve considerable success in newborn management with due respect to both medical treatment and general care, especially in the group of neonates with low body weight at birth [1]. At the same time, neonatal sepsis in the early period still predetermine sickness and mortality of newborns [2, 3]. Thus, the role of sepsis, pneumonia and meningitis constitutes practically 23.4 % of all the lethal cases of newborns [4].

At the same time, development of sepsis in neonates is associated with not only with the risk of neonatal death but with remote consequences as well and nervous-psychic development in particular. A high rate of neonatal mortality is caused both by certain difficulties in diagnostics and complicated prevention and treatment in the neonatal period [5]. It is explained by the fact that clinical signs of infectious pathology both in term and preterm infants are minimal, obliterated and nonspecific. They can be provoked by non-infectious causes promoting the development of tachypnea of newborns, thermal imbalance under the influence of environmental factors, apnea of preterm neonates and other numerous clinical syndromes [6]. Insufficient information value of

clinical-anamnesis findings in detection of neonatal infection stipulates the necessity to find laboratory characteristics enabling to identify severe life threatening pathology during the first stages of its development. In recent times neonatologists have set their great hopes on detection of proteins of acute inflammatory phase and anti-inflammatory cytokines in the blood of neonates as reliable markers of neonatal infection [7, 8]. Thus, C-reactive protein is synthesized by the liver under the effect of interleukin-6 and interleukin-1β. An exact function of C-reactive protein is unknown now, although it has been found to activate the complement and effects phagocytes by means of interaction with receptors to immunoglobulins. Only trace concentrations of this protein are found in the blood plasma within the norm. Its concentration 10 mg/L and more is most often used as a point of distribution to detect infection. The secretion of C-reactive protein is found to be initiated 4–6 hours after stimulation, and its peak concentration value in the blood is observed 36–48 hours later. In case the stimuli of an acute phase stop the concentration of this protein becomes 50 % less every day [9]. The diagnostic value of C-reactive protein in detection of neonatal infection is found to increase considerably in case serial examinations are performed [10].

A great role in early response of the body to infection is played by interleukin-6 (IL-6). Its concentration of the blood increases dramatically under the influence of microorganism antigens. It occurs earlier than C-reactive protein content in the blood increases. An increased level of IL-6 content in the umbilical cord blood of a neonate in the very first hours of life is a high diagnostic value test to detect early neonatal infection. However, due to a quick degradation of this cytokine its concentration in the blood under effect of treatment decreases quickly and becomes practically indefinite in the majority of infected newborns at the end of the second day of their lives [11].

Interleukin-8 (IL-8) synthesis occurs by activated monocytes in response to bacterial invasion in the infant body. This pro-inflammatory response does not depend considerably on gestation and postnatal age of a child. Interleukin-8 content in the blood of both term and preterm newborns is reliably higher in case infectious diseases available as compared to neonates with non-infectious pathology [12].

**2. Aim of research**

Aim of our investigation was to study diagnostic value of interleukin-6 and 8, and C-reactive protein contents in the blood serum of newborns on the second day of their lives in case susceptibility factors to the development of infectious-inflammatory process were available.

**3. Materials and methods**

By means of simple consistent sampling method a group of newborns at the end of the first-beginning the second day of their lives was formed. The babies were born in Chernivtsi Maternity Home during 2016–2017 years. The inclusion criteria were: age of the first 1–2 days of life, continuous collection of patients, same maternal institution, availability of susceptibility factors to early neonatal infection from maternal and neonatal sides considering specific susceptibility factors, availability of clinical signs of organ dysfunction provoked by both infectious and non-infectious causes.

The exclusion criteria were: available risk factors of early neonatal infection except prematurity, conducing intrauterine prevention of infection caused by B group streptococcus [13]; availability of congenital developmental defects and exchange mistakes; availability of clinically valuable inherited diseases in family anamnesis which signs could simulate infection.

A comprehensive clinical-laboratory examination was carried out in the group of 100 newborns formed considering all the above inclusion and exclusion criteria at the end of the first – beginning of the second day of their lives.

Among the examined infants there were 57 boys, 43 girls, including 49 urban and 51 rural residents. The families involved in the study were distributed by their social status in the following way: 21 % office workers, 10 % industrial workers, and 69 % unemployed. According to marital status there were 80 married women and 20 unmarried ones. Mother's age >35 years was detected in 9 cases, father's age >40 years – in 3 cases.

By their gestational age the patients were distributed in the following way: less than 37 weeks – 34 newborns including 14 – with gestational age, ≤34 weeks 2 newborns – with gestational age of

31 weeks. Gestational age of more than 42 weeks was registered only in 2 newborns, 64 babies were born in term. The body weight at birth ≤2500 g was registered in 34 newborns including those with the body weight ≤2000 g – in 10 and ≤1500 g – in 3 babies. The body length ≤47 cm was registered in 34 newborns including those with their body length ≤45 cm in 19 babies, ≤43 cm – in 6 newborns, ≤40 cm – in 2 newborns. Head circumference ≤34 cm was registered in 72 patients including 21 newborns with ≤31 cm and 3 babies – ≤29 cm. Chest circumference ≤31cm was registered in 35 newborns including those with ≤29 cm – in 22 babies and ≤26.7 cm – in 3 newborns.

Among the examined newborns 18 patients were practically healthy, the risk of intrauterine infection realization was found in 25 newborns, 2 neonates were with retarded intrauterine development, hypoxic-ischemic lesion of the central nervous system was registered in 14 neonates. Hemorrhages in the cerebral ventricles were registered in 3 patients, development of post-asphyxia syndrome – in 2 newborns. 16 children were born to mothers with verified TORCH-infection. Pneumonia was diagnosed in 7 newborns, sepsis – in 4 babies, 1 child was afflicted with pyelonephritis and 1 more – with pronounced pyoderma. Associated infectious and non-infectious pathology was registered in 7 children.

During the 1st minute of their life 83 neonates were evaluated by Apgar score ≤ 7 points. 11 babies among them got <5, and < 3–5 newborns. On the 5th minute evaluation by Apgar score was: 55, 3 and 1 cases respectively.

The design of the investigation assumed the analysis of the results of a comprehensive examination of newborns with the estimation of C-reactive protein content in the blood serum by means of the reagents produced by Ltd "Impek" [14], and estimation of IL-6 and IL-8 concentration in the blood serum by means of immune-enzyme analysis (IEA) [15].

The data obtained were analyzed by means of biostatistics methods applying the principles of clinical epidemiology with the use of the computer packages "STATISTICA" StatSoft Inc. and Excel XP for Windows on a personal computer using parametrical and non-parametrical methods of calculation [16].

The protocol of examination of children was compiled according to the main principles of Helsinki Declaration on Biomedical Research (1974), adapted on the 41th International Assembly in Hong Kong (1989) and the Belmont Report (1979).

**4. Results**

Clinical symptoms and signs caused by infectious-inflammatory process and/or conditions simulating it were found in 82.0 % of newborns in the period of acute adaptation (on the first – beginning the second day of life). Thus, among them fever was found in 25.8 % cases; inhibited sucking – in 79.4 %; a „sick child" – 89.4 % and swellings – 16.5 %.

The data presented were indicative of the fact that those most frequently occurred disorders could be caused by both infectious diseases and non-infectious pathological conditions of the early neonatal period. Undoubtedly, it complicates detection of early neonatal infection with the use of exclusively systemic clinical signs.

Digestive disorders in the form of vomiting and regurgitation were registered in 6.2 % of newborns, and hepatomegaly – in 12.0 % of cases.

Respiratory changes presented a larger spectrum of clinical signs. Thus, neonates with cyanosis constituted 78.4 %, dyspnea was registered in 13.4 % of cases, chest retraction – 25.8 %, and grunting – 12.4 %.

The data presented enabled to consider that among clinical signs associated with pathology of the respiratory system there were various variants of cyanosis most often. At this period of life they can be caused not only by infectious but non-infectious pathology as well, and at the same time they can reflect the process of adaptation of a newborn. More specific symptoms of respiratory lesions were registered much rarely. They may include dyspnea and apnea with pathological character, that is, were characterized by the availability of clinical signs of blood gas content disorders and duration of the course.

Retraction of compliant areas of the chest in association with tension of the nasal wings and grunting breathing occurred considerably rare, although from the clinical point of view they were

more important in detection of pathology of the respiratory system. Indicated clinical symptoms characterize not only availability of early neonatal infection and congenital pneumonia in particular [2], but were caused by non-infectious pathology.

Clinical signs of functional disorders in the circulatory system were most frequently manifested by pale skin, „motley", cool skin on the peripheral areas (15.5 %), tachycardia (9.3 %), systemic arterial hypotension (6.2 %) and bradycardia (7.2 %). Similar to respiratory disorders those signs could be caused by both an infectious process and pathology of newborns simulating it.

Changes from the hemopoiesis in the examined children were mostly manifested in the form of moderate jaundice (12.4 %), pale skin (20.6 %) and petechial skin rash (8.2 %). Similar to the above clinical signs and symptoms hemopoietic changes could be caused by both infectious and non-infectious factors.

On the central nervous system side the following signs prevailed: hyporeflexia (94 %), tremor and convulsions (25.8 %), behavioural changes (15.5 %) and "high-pitch" cry (12.4 %). Similar to all the above clinical signs and symptoms those neurological symptoms cannot be considered characteristic only for infectious-inflammatory processes, therefore they cannot be used alone to verify it in the examined newborns.

At the same time it should be noted that clinical signs found possessed a reliable moderate positive connection with verified infection of newborns. Thus, general signs of disorders of a child condition correlated with infectious pathology available with a moderate reliable positive connection ($r=0.51$, $P=0.001$). Changes in the digestive system possessed a little bit less connection ($r=0.47$, $P=0.001$). Correlation of changes in the cardio-vascular system with verification of infectious pathology was detected on the same level ($r=0.42$, $P=0.001$), and a little less connection with disorders of the central nervous system ($r=0.24$, $P=0.02$). The most powerful correlation relations were detected with verified infectious pathology of the changes found in the respiratory system ($r=0.52$, $P=0.001$).

At the same time the combination of presented clinical signs with factors of susceptibility to infectious diseases from maternal and neonatal sides and considering specific factors increased the power of such relations considerably ($r=0.64$, $P=0.001$).

Therefore, in spite of the fact that examined children presented neither specific nor pathognomonic signs of infectious-inflammatory pathology in the first day of life, it could be suggested that evaluation of these parameters considering the results of paraclinical examination with detection of acute inflammatory phase proteins and pro-inflammatory cytokines are able to increase the efficacy of diagnostic process as to the detection of early neonatal infection.

An average content of IL-6 in the blood serum of the examined children was found to be 44.6±7.7 pg/ml. **Fig. 1** presents the registration frequency of various concentrations of IL-6 (pg/ml) in the blood serum of the examined children.

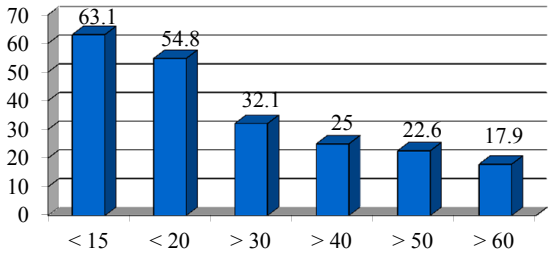


**Fig. 1.** Registration frequency of various concentrations of IL-6 (pg/ml) in the blood serum of the examined children (in %)

The data obtained substantiate that low concentrations of IL-6 prevail, and therefore the mentioned "pro-inflammatory" mediator hardly can be used to verify early neonatal infection. We have not found a reliable correlation connection between IL-6 content in the blood serum and clinical signs of available infectious-inflammatory process in the neonates. At the same time, the content of this cytokine in the blood serum of a child possessed a powerful reliable correlation con-

nection with available unfavourable course of previous pregnancies in the mother (r=0.77, P=0.001) and a week positive connection with available infectious pathology in the mother (r=0.26, P=0.03).

An average IL-8 content in the blood serum of the examined children was 87.5±15.3 pg/ml. **Fig. 2** presents the registration frequency of various concentrations of IL-8 (pg/ml) in the blood serum of the examined children.

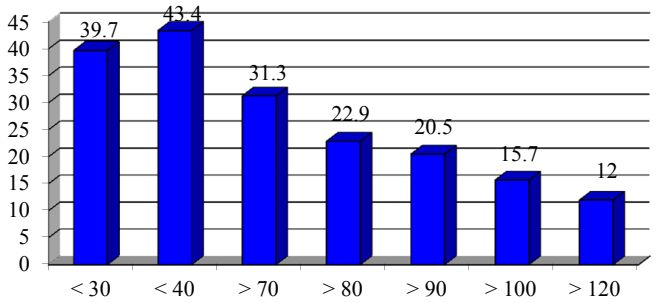


**Fig. 2.** Registration frequency of various concentrations of IL-8 (pg/ml) in the blood serum of the examined children (in %)

The data obtained substantiate that low concentrations of IL-8 prevail in the blood serum of the examined children. It enables to suggest that the above parameter could hardly possess sufficient diagnostic value to detect early neonatal infection. It might be explained by the fact that increased content of this inflammatory mediator in the blood serum reflects severe disorders of the general condition of a child, but not the activity of infectious-inflammatory process. It is indirectly evidenced by the fact that between the concentration of this pro-inflammatory cytokine in the child's blood serum there is a reliable reverse correlation relation with the evaluation of the child by Apgar score on the 1st minute of life (r=–0.42, P=0.02), and a positive relation with severe disorders of the child's general condition in the course of treatment in the hospital (r=0.51, P=0.004), as well as verification of an infectious disease (r=0.46, P=0.01).

An average content of C-reactive protein in the blood serum of the examined children was 46.5±2.9 mg/L. **Fig. 3** presents registration frequency of different concentrations of C-reactive proteins (mg/L) in the blood serum of the examined children.

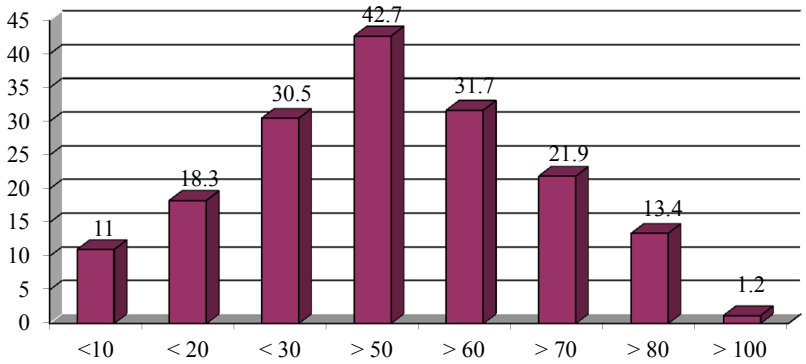


**Fig. 3.** Registration frequency of different concentrations of C-reactive proteins (mg/L) in the blood serum of the examined children (in %)

The data obtained give the evidence to consider that although in the majority of children C-reactive protein elevated the concentration of 10.0 mg/L which is traditionally considered to be a discriminant as to the verification of an infectious process in newborns [7]. Normal distribution of the concentration in the population of the children examined gives the evidence to consider that this diagnostic test will possess a high specificity with its orientation toward its rather high concentration. It was indirectly evidenced by the fact that C-reactive protein concentration in the blood serum possessed only weak although reliable correlation relation with verification of early neonatal

infection of newborns (r=0.25, P=0.025). A stronger correlation might be absent due to the fact that synthesis of this acute inflammation phase protein is mostly modeled by mother's condition [15], evidenced by a reverse reliable correlation relation between it and cultural-behavioural and medical factors of a pregnant woman reflecting susceptibility to early neonatal infection (r=-0.48, P=0.046).

Diagnostic value of detection of C-reactive protein content under conditions of its concentration more than 10.0 mg/L was characterized by the following indices: sensitivity 65 %, specificity 79 %, positive predicted value 66 %, negative predicted value 78 %, positive index of likelihood 3.0 and negative index of likelihood 2.3. It should be noted that according to our obtained data the indices of diagnostic value in detection of C-reactive protein level were somewhat lower than it had been registered in certain literary sources. Therefore this index was evaluated in the groups of term and preterm babies. While detecting diagnostic value of C-reactive protein content among term newborns the parameters of sensitivity were 80 %, specificity – 96 %, positive index of likelihood – 12.8 %, negative index of likelihood – 4.1 %. In the group of preterm babies these indices were 43 %, 68 %, 1.4, 1.2 respectively, which can be associated with a considerable amount of false negative results in the group of preterm babies.

Depending on the point of distribution diagnostic value of acute phase indices of the inflammatory process was made in confirming neonatal infection. The results obtained are presented in **Table 1**.

**Table 1**

Diagnostic value of tests (%) to confirm infection

| Indices | Sensitivity | Specificity | Positive predicted value | Negative predicted value | Index of likelihood+ | Index of likelihood– |
|---|---|---|---|---|---|---|
| IL-6>60 pcg/ml | 23 | 85 | 59 | 52 | 1.5 | 1.1 |
| IL-8>70 pcg/ml | 34 | 70 | 53 | 51 | 1.1 | 1.1 |
| **C**-RP>60 mg/L | 41 | 74 | 60 | 55 | 1.6 | 1.3 |

High indices of specificity and positive predicted value were found to be indicative of the availability of infectious-inflammatory process of newborns. At the same time this constellation practically in every second child was associated with false negative results.

**Table 2** presents evaluation of diagnostic value of acute phase indices of the inflammatory process in disproving neonatal infection.

**Table 2**

Diagnostic value of tests (%) in disproving infection

| Indices | Sensitivity | Specificity | Positive predicted value | Negative predicted value | Index of likelihood + | Index of likelihood– |
|---|---|---|---|---|---|---|
| IL-6<20 pcg/ml | 58 | 48 | 53 | 53 | 1.2 | 1.1 |
| IL-8<20 pcg/ml | 28 | 69 | 48 | 49 | 1.1 | 1.1 |
| **C**-RP<10 | 14 | 94 | 70 | 52 | 2.3 | 1.1 |

## 5. Discussion

Low indices of both positive and negative predicted values of the applied immunologic tests demonstrate that they should not be used independently to disprove EOS in the examined patients. This conclusion contradicts the literary data [11, 18], but it can be explained by the fact that at the end of the first-beginning the second day of life physiological "crossing" occurs in the synthesis of IL-6 and C-reactive protein, and IL-8 at this period of life not only decreases in the blood serum physiologically but its concentration is mainly determined by the severity of general body condition irrespective of the cause – infectious or non-infectious factor.

Therefore, analysis of diagnostic value of certain immunologic tests to verify early neonatal sepsis demonstrated that all of them in the majority of cases had moderate specificity, but their

application is associated with a high rate of false negative results with low prognostic value of a negative test. On the assumption of this, considering odds ratio, we can state that none of the test can be used itself to confirm or disprove early neonatal sepsis. Due to this fact, these tests rather enable to approve antibiotic administration in neonates with suspected early neonatal sepsis, than give the ground against antibacterial therapy in case of conditions simulating sepsis. Actually, the indicated diagnostic value of the given immunologic markers of neonatal sepsis in the first days of life cannot satisfy neonatologists and make them search for new, more informative biomarkers of early generalized infection. Thus, according to certain literary data [19, 20] the use of procalcitonin blood test possesses rather sufficient for population studies sensitivity – 81 % (74–87 %) and specificity – 79 % (69–87 %). Although its value in every certain case decreases due to the fact that its increased content in the blood of neonates is possible in case of a number of infectious diseases often found in the first days of life and can simulate sepsis (respiratory distress-syndrome, intraventricular hemorrhages, unstable hemodynamics, etc.). Therefore, to determine neonatal sepsis procalcitonin blood test is recommended to be made together with C-reactive protein, since this combination today is considered to be so-called "gold standard" in neonatology.

Detection of presepsin [21, 22] in the blood of neonates is considered to be perspective to confirm early neonatal sepsis, since its level increases during first 1.5–2 hours after phagocytosis induction. Sensitivity and specificity of this test to find early neonatal sepsis are on an average 80 %, that is, probability of both false positive and false negative results of the test is detected in every fifth child. The diagnostic value of procalcitonin and presepsin blood tests to determine early neonatal sepsis requires from the researchers to find more informative biomarkers. And till expectations concerning "gold standard" in neonatology are not justified, this pathology should be diagnosed from the positions of an integral assessment of comprehensive examination indices, and in the form of PIRO conception in particular.

**6. Conclusions**

1. None of the clinical signs associated with infectious-inflammatory process in newborns in the first two days of their life enabled to verify reliably availability of systemic bacterial infection.

2. None of the paraclinical indices demonstrated high diagnostic value concerning confirmation of systemic bacterial infection in newborns in the first two days of life.

3. Clinical-paraclinical signs associated with infectious-inflammatory process in newborns in the first two days of their life should be considered together with the SIIOD system (susceptibility, infection, inflammation, organ dysfunctions).

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