CHILDREN WITH EXTREMELY LOW BODY WEIGHT: CLINICAL CHARACTERISTICS, FUNCTIONAL STATE OF THE IMMUNE SYSTEM, PATHOGENETIC MECHANISMS OF THE FORMATION OF NEONATAL PATHOLOGY

Monograph

Under the editorship of:

Chistyakova G. N., Ustyantseva L. S., Remizova I. I.

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The purpose of the monograph, which contains a modern view of the problem of adaptation of children with extremely low body weight, is to provide a wide range of doctors with basic information about the clinical picture, functional activity of innate and adaptive immunity, prognostic criteria of postnatal pathology, based on their own research. The specific features of the immunological reactivity of premature infants of various gestational ages who have developed bronchopulmonary dysplasia (BPD) and retinopathy of newborns (RN) from the moment of birth and after reaching postconceptional age (37-40 weeks) are described separately. The mechanisms of their implementation with the participation of factors of innate and adaptive immunity are considered in detail. Methods for early prediction of BPD and RN with the determination of an integral indicator and an algorithm for the management of premature infants with a high risk of postnatal complications at the stage of early rehabilitation are proposed. The information provided makes it possible to personify the treatment, preventive and rehabilitation measures in premature babies. The monograph is intended for obstetricians-gynecologists, neonatologists, pediatricians, allergists-immunologists, doctors of other specialties, residents, students of the system of continuing medical education.

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LIST OF ABBREVIATIONS

IVH	intraventricular hemorrhage
IUI	intrauterine infection
GIT	Gastrointestinal tract
ALV	artificial lung ventilation
CI	cervical incompetence
ELISA	enzyme-linked immunosorbent assay
INF	interferon
ABB	acid-base balance of blood
UBFD	uteroplacental blood flow disorder
CPI	chronic placental insufficiency
NSG	neurosonography
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
PCA	postconceptional age
GA	gestional age
PACNS	perinatal affection of the central nervous system
RDS	respiratory distress syndrome
BPD	bronchopulmonary dysplasia
IGRS	intrauterine growth restriction syndrome
US	ultrasound
CPI	chronic placental insufficiency
CMV	cytomegalovirus
CNS	central nervous system
IVF	in vitro fertilization
ELBW	extremely low body weight
HRFDA	hemodynamically relevant functioning ductus arteriosis
ROP	retinopathy of prematurity
BEecf	buffer bases in extracellular fluid
CPAP	constant positive airway pressure
HCO_{3ct}	standard bicarbonate
IFN-γ	interferon gamma
CD	cluster of differentiation
HLA-DR	numan leucocyte antigens
MHC	major histocompatibility complex
TNF	tumor necrosis factor
NK	natural killer cells
Ig	immunoglobulin
IL	interleukin
PaO_2	partial arterial oxygen tension
$PaCO_2$	partial tension of carbon dioxide in arterial blood
SaO_2	oxygen saturation of arterial blood

INTRODUCTION

The birth of deeply premature babies with extremely low body weight (ELBW) is the most topical issue in modern perinatology due to the high risk of morbidity and mortality, despite the fact that the proportion of births with a gestational age of less than 32 weeks, as a rule, does not exceed 1.5- 2% [1, 2, 3, 4, 5]. According to foreign sources, the survival rate of this category of children over the past twenty years has significantly increased from 42 to 76% [6]. In recent years, there has been a decrease in the proportion of severe complications in children with EBMT against the background of improving organizational and medical technologies for nursing deeply premature babies, the quality of prenatal follow-up [7, 8]. However, the rates of chronic pathology and disability do not show a significant downward trend and remain high even in developed countries [9, 10, 11].

Functional immaturity of the respiratory, cardiovascular, immune, and central nervous systems (CNS) is prevalent among deeply premature newborns, which leads to a high susceptibility of children to the development of pathological conditions and is the cause of a high level of morbidity [12]. Undoubtedly, the improvement of methods of primary resuscitation care and respiratory support (sparing modes of artificial lung ventilation, preference for non-invasive ventilation with a decrease in oxygenation parameters), early use of a surfactant, improvement of neonatal care technologies, significantly improved prognosis of long-term postnatal use of corticosteroids 13, 14, 15, 16].

The child's immune system plays a leading role in the pathogenesis, clinical course and outcome of hypoxic and infectious diseases, which largely determines the possibility of full rehabilitation of premature babies [17, 18]. In recent years, the role of the cytokine cascade has been actively studied in the development of pathology of the perinatal period. The theory of imbalance of pro- and anti-inflammatory cytokines is considered both in the pathogenesis of the infectious process [18, 19, 20] and in non-infectious post-hypoxic conditions [21, 22]. A large part of scientific research is devoted to assessing the state of adaptive immunity [23, 24], while data on the functioning of the innate link of immunity are presented fragmentarily. However, it is the immunocompetent cells of inborn immunity that are the main ones in the formation of protection against bacterial complications and the formation of immune dysfunction.

In connection with the peculiarities of the immunological resistance of children with EBMT, the leading cause of death along with serious injuries of the CNS are infectious and inflammatory diseases [25]. In modern works, much attention is paid to the stage of nursing children with EBMT in the conditions of the intensive care unit [23, 26]. However, there are few works devoted to the study of this category of children at the stage of early rehabilitation, taking into account the characteristics of inborn and adaptive immunity at the systemic and local levels,

depending on the gestational age. Against the background of a deficiency of humoral protection factors, markers of nonspecific resistance, insufficiency of inborn and adaptive immunity, increased infectious morbidity in children with EBMT, it is important to study the mechanisms of development of postnatal complications from the standpoint of clinical and immunological adaptation of a premature baby, which was the purpose of writing this monograph.

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Chapter I. RISK FACTORS OF BIRTH OF PREMATURE CHILDREN

1.1. Social and medical problems of childbirth to children with extremely low body weight

The gradual transition of the constituent entities of the Russian Federation (RF) to new technologies for nursing children with ELBW is a natural stage in the development of Russian perinatology, regulated by order No. 1687n dated December 27, 2011. From this moment on, the state registration of newborns with a body weight of 500 g at a gestational age of 22 weeks or more began in accordance with the birth criteria recommended by the World Health Organization (WHO), as well as the introduction of organizational and medical technologies for nursing deeply premature babies, improving the quality of prenatal observations [1, 2, 3]. In this regard, effective nursing and rehabilitation of newborns with ELBW is a task set for the constituent entities of the Russian Federation, the solution of which will lead to a decrease in perinatal and infant mortality, and will improve the quality of further development.

According to the WHO recommendations, a child born in a preterm birth from 22 to 37 weeks is considered premature. According to the classification of premature birth, adopted in 1993 in the Russian Federation, depending on the gestational age, superearly (22-27 weeks), early (28-33 weeks) and premature birth (34-37 weeks) are distinguished. According to the body weight at birth, according to the WHO classification, 10 revisions distinguish groups of children up to 2500 grams i.e. from low, up to 1500 grams - from very low and up to 1000 grams of extremely low body weight.

In recent years, the frequency of preterm birth on average in developed countries is 5-10%, in the world - 15% [1, 27], of which 1-1.8% is the share of children with VLBW, 0.4-0.5% - children with ELBW [4].

In many works, much attention is paid to the analysis of the reasons leading to the premature birth of children, the state of physical and neuropsychic development of newborns [5, 6, 7, 8], as well as genetic factors that contribute to premature birth, which are realized both by the mother and and a child. In addition to genetic factors, infectious and endocrine diseases, aggravated obstetric -gynecological history, preeclampsia, multiple pregnancy, chronic placental insufficiency (CPI), placental abruption [4, 9]. According to Russian researchers, there has been an increase in the number of women carriers of TORCH infections, which affect the fetation throughout pregnancy [10].

The leading place among the problems concerning children with ELBW are survival and mortality rates [8, 11, 12]. Modern approaches to perinatal care in Russia and in the world have increased the survival rate of newborns with ELBW up to 45% [13, 14].

The percentage of unfavorable outcomes among surviving children also depends on birth weight and reaches 40-50% in newborns with a weight of 750 to 1000 g, rising to 70-90% at the birth of children weighing from 500 to 749 g, which are, undoubtedly the most vulnerable and difficult contingent for rehabilitation [15, 16, 17]. According to world statistics, among newborns, 11.6% of children under 500 g, 50.7% - from 500 to 749 g, 83.9% - from 750 to 1000 g at birth survive [8, 18]. It is believed that newborns weighing from 500 to 749 g are in the "zone of the viability limit" and their nursing is very problematic. According to American perinatologists, the survival rate of newborns with a gestational age of 22-24 weeks before discharge from the hospital averages 13%, and with a gestational age of more than 26 weeks - 70%, in the future 70% and 30% of children have severe CNS damage, respectively [19]. In Japan, in 2011, the mortality rate of newborns with gestational ages of 22 and 23 weeks was 80% and 64%, respectively [20].

A study by V. Fellman et al. (2009) showed that in Sweden, by one year of age the survival rate among newborns at a gestational age of 22 to 26 weeks was 70%, with 9.8% of children born at 22 and 85% at 26 weeks of gestation. The authors note the absence of serious somatic and neurological complications in 45% of premature infants with ELBW [21]. Over the past two decades, the survival rate of newborns with ELBW has increased in Italy (from 42% to 76%). However, the percentage of the formation of bronchopulmonary dysplasia remains approximately at the same level, amounting to 30.5% and 39%, respectively [22].

The literature indicates a natural relationship between the mortality of children with ELBW and postnatal age. A study by T. Nakhla et al. [23], demonstrated that 49% of newborns with ELBW died in the 1st week of life, 17% - in the 2nd week and only 9% after the 2nd month of life. According to M.A. Mohamed (2010), the survival rate of premature newborns with birth weight from 500 to 750 grams increased to 70% with survival in the first three days and up to 80% - until the end of the 1st week of life [24]. According to the research results of H.V. Bashmakova et al. (2012) the mortality rate of children born with a body weight of 500 to 750 grams was 54.8%, from 750 to 1000 grams - 11.5%. Moreover, the mortality rate of premature babies in the 1st group at the 1st week of life was five times higher than in the 2nd group [8].

The reason for the high incidence of premature infants is the functional immaturity of the respiratory, cardiovascular, immune, and central nervous systems (CNS), which makes premature infants susceptible to the development of pathological conditions [25]. In connection with the peculiarities of the immunological resistance of deeply premature infants, the leading cause of death along with serious injuries of the central nervous system are infectious and inflammatory diseases [26]. Along with infectious and inflammatory pathology, the authors include respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), left ventricular failure and systemic hypotension, hemodynamically relevant functioning ductus arteriosis (HRFDA) [27, 28, 29, 30, 31].

In recent years, there has been a decrease in the proportion of severe complications in children with ELBW [21, 28]. However, the rates of chronic pathology and disability do not show a significant tendency to decrease and remain high even in developed countries [32, 33, 34].

Children with ELBW are born in a serious condition, being maximally exposed to complications associated with prematurity. Therefore, their nursing refers to high-tech care, since they need support for all basic vital functions of the body [4]. Numerous studies confirm that in order to reduce perinatal and infant mortality, a favorable prognosis for the further development of deeply premature newborns in order to provide comprehensive high-tech medical care for women in high-risk groups, hospitalization is required in specialized perinatal centers of III level, where the neonatal intensive care unit operates [35, 36, 37, 38].

Measures to prevent premature birth are more effective than efforts to intensive care and rehabilitation of deeply premature babies even taking into account the modern level of diagnostic and treatment technologies [29]. Prevention of unfavorable outcomes in children with ELBW requires long-term and expensive rehabilitation treatment. Therefore, given the low health potential of children with ELBW, the high incidence of pathology and the low quality of life, the main reserves for reducing the incidence and mortality of deeply premature babies are full monitoring of pregnant women, the identification of high-risk groups and the use of modern nursing technologies in perinatal centers [29].

In large world perinatal centers with the ability to provide qualified high-tech care, 80-85% of newborns with ELBW and VLBW survive and leave these centers, this indicator varies widely depending on the body weight and gestational age of the child [39]. Subsequently, from 2 to 5% of them die within the first two years after discharge from delayed complications. Unfavorable outcomes of children born at 22-25 weeks of gestation are also noted by Russian authors [40, 41]. Researchers believe that in the indicated time frame there is a certain biological barrier that impedes the survival of newborns [8, 35]. To increase survival rates and minimize residual complications of diseases of the prematurity period in the Russian Federation, a three-stage system of nursing premature babies has been adopted in specialized perinatal centers:

Stage I - provision of primary resuscitation care in the delivery room, nursing in the NICU;

Stage II - nursing in specialized departments of pathology of premature infants of perinatal centers (stage of early rehabilitation);

Stage III - dispensary observation in a children's polyclinic, rehabilitation in the early recovery period in a day and round-the-clock hospital.

Despite the increase in the survival rate of such children, the risk of neurological impairment and cognitive impairment remains high [33, 31, 42, 43, 44]. The number of healthy newborns with ELBW does not exceed 10-25%, and the percentage of severe neurological outcomes ranges from 12 to 32% [24, 44].

In France, disability is much more often registered in children born at a very early preterm birth compared with children born at an early preterm birth (infantile cerebral paralysis (ICP) was 20% in children with a gestational age of 24-26 weeks and only 4 % at 32 weeks) [46].

In most modern works, much attention is paid to the stage of nursing children with ELBW in the conditions of the intensive care unit [47, 48, 49]. However, there are not enough publications in the literature devoted to the study of premature babies at the stage of early rehabilitation, where newborns are transferred after stabilization of the state and restoration of basic vital functions, due to the need for long-term respiratory support of morphofunctionally immature lungs, which dictates the need for further research.

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1.2. Perinatal risk factors for the birth of premature infants

To identify a complex of unfavorable factors of ante- and intranatal nature that caused the birth of premature infants with extremely low body weight, the obstetric and gynecological history, features of the gestational period and childbirth were studied in 114 women hospitalized at the FSBI "The Ural Research Institute of Maternity and Child Care" The Ministry of Health of the Russian Federation. This study was approved by the local ethics committee of the institute. We received informed voluntary consent from all women for the processing of personal data, treatment, examination.

The classification of preterm birth, adopted in 1993 in the Russian Federation, in which, depending on the gestational age was fundamental in the division of the groups, the following groups were identified:

1st group – early childbirth (22-27 weeks, the weight of the baby is within 500-999 grams)

2nd group – premature birth (28-33 weeks, 1000-2000 grams)

3rd group – full-term pregnancy (37-40 weeks, 2500 grams or more)

All surveyed women were comparable in age. The average age of women in groups 1 and 2 was: 30.13 ± 5.66 years and 30.27 ± 6.11 years, respectively. In the group of women who gave birth to full-term newborns, this indicator was slightly lower - 29.41 ± 2.97 years ($p_{1-3, 2-3}$>0,05). Most of the mothers of all groups had a permanent place of work (63 %, 74,4 %, 96 %, p_{1-2}>0,05, $p_{1-3,2-3}$<0,005). Less than half of women who gave birth at the time of very early preterm birth were married (47.8% and 60.5% in groups 1 and 2, 84% in the comparison group (p_{1-2}>0,05, =0,002 p_{2-3}=0,015)) and less than a third lived in the city (23.9% in the 1st, 30% in the 2nd and 28% in the comparison group). Bad habits, such as nicotine addiction and alcohol consumption, were not practically observed (4.34% in the 1st, 4.65% in the 2nd and 0% in the comparison group).

The structure of extragenital pathology is shown in Table 1.

Table 1.

The structure of extragenital pathology of mothers in premature infants

Class of diseases according to ICD-10	1st group (women who gave birth to children at 22-27 weeks' gestation period, n = 46)		2nd group (women who gave birth to children at 28-31 weeks' gestation period, n = 43)		3rd group (women who gave birth to full-term babies, n = 25)		p
	abs	%	abs	%	abs	%	
Class I. Certain infectious and parasitic diseases	4	8,69	6	13,95	0	0	
Class II. Neoplasms (fibroids)	1	2,17	7	16,27	1	4	p_{1-2}=0,026,
Class III. Diseases of the blood and blood-forming organs (mild to moderate anemia)	11	23,91	13	30,23	6	24	
Class IV. Diseases of the endocrine system, nutritional disorders and metabolic disorders (including):	9	19,5	14	32,56	0	0	p_{1-3}=0,017 p_{2-3}=0,00005
Obesity	0	0	10	23,25	0	0	$p_{1-2,2-3}$=0,00093
Type I diabetes mellitus	0	0	1	2,32	0	0	
Hypothyroidism	9	19,5	3	6,97	0	0	p_{1-3}=0,017
Class VII. Diseases of the eye and adnexa	12	26	8	18,6	8	32	
Class IX. Diseases of the circulatory system	4	8,69	11	25,58	0	0	p_{1-2}=0,04 p_{2-3}=0,0004
Class XI. Diseases of the digestive system	6	13	7	16,2	3	12	
Class XIV. Diseases of the genitourinary system	6	13	9	20,93	0	0	

Note. *In connection with the identification of several pathological signs in the same woman, the total number of cases exceeds 100%, p1-2, p1-3, p2-3 - the significance of differences between groups of mothers (χ2 test with a Yates correction): 1 - mothers, those who gave birth to children at 22-27 weeks' GP, 2 - mothers who gave birth to children at 28-31 weeks' GP, 3 - a comparison group.*

Extragenital pathology is an unfavorable background that affects the capabilities of adaptive mechanisms, the limitation of which, in turn, leads to complications of pregnancy, childbirth and the postpartum period. The morbidity patterns of women who gave birth to children with ELBW was characterized by a high frequency of extragenital pathology. Hypertension was recorded significantly more often in women of the second group - in 25.68% versus 8.69% of cases in the first group ($p_{1-2} = 0.04$).

HIV infection was noted in the anamnesis of two women of the main groups.

Comparative analysis of maternal medical history data showed an extremely unfavorable course of the antenatal period (Table 2).

Table 2.

Obstetric history of the mothers of the observed children

Nosological form	**1st group (women who gave birth to children at 22-27 weeks' gestation period, n = 46)**		**2nd group (women who gave birth to children at 28-31 weeks' gestation period, n = 43)**		**3rd group (women who gave birth to full-term babies, n = 25)**		**p**
	abs	**%**	**abs**	**%**	**abs**	**%**	
Agenesia	4	8,69	1	2,32	0	0	$p_{1-2,1-3,2-3} \geq 0,05$
Justifiable artificial abortion	20	43,47	23	53,48	7	28	$p_{1-2,1-3,2-3} \geq 0,05$
Miscarriage	2	4,34	3	6,97	1	4	$p_{1-2,1-3,2-3} \geq 0,05$
Regression	2	4,34	2	4,65	2	8	$p_{1-2,1-3,2-3} \geq 0,05$
Spontaneous miscarriages	10	21,73	9	20,93	4	16	$p_{1-2,1-3,2-3} \geq 0,05$

Note: *p1-2, p1-3, p2-3 - the significance of differences between the groups of mothers (χ2 test with a Yates correction): 1 - mothers who gave birth to children at 22-27 weeks' GP, 2 - mothers who gave birth to children at 28-31 weeks' GP, 3 - comparison group.*

More than 60% of all women were re-pregnant (71.44%, 67.44% and 60% of cases). A burdened obstetric history was noted in half of the women examined, the leading factors were spontaneous miscarriages and induced abortions, no significant differences were found between the compared groups. Spontaneous miscar-

riages were recorded in every fifth woman in the main groups and in every sixth comparison group ($p_{1-2,1-3,2-3} \geq 0,05$). Artificial terminations of pregnancy among women with preterm birth were 1.55 and 1.91 times more frequent than women who gave birth to full-term infants. Agenesia (primary, secondary) in women who gave birth to children of gestational age of 22-27 weeks was diagnosed 3.75 times more often than in group 2. In the comparison group, this pathology was not registered. There were no significant differences in the incidence of regressing pregnancies in mothers of children of both groups. The onset of pregnancy by assisted reproductive technologies (ART) was noted in 2 and 3 cases among women in the main groups. In women in the comparison group, pregnancies occurred without medical intervention.

Among the complications of pregnancy in women of the main groups, preeclampsia of moderate severity was more common ($p_{1-2} \geq 0,05$, $p_{1-3}=0,02$, $p_{2-3}=0,005$), its severe coursesw was observed only in every eighth patient (Table 3).

The threat of termination of this pregnancy was diagnosed in more than half of the women in the main groups. Chronic placental insufficiency (CPI) was more often observed in a subcompensated form ($p_{1-3}=0,003$, $p_{2-3}=0,0001$, $p_{1-2} \geq 0,05$), in the comparison group there was only a compensated form in one woman.

Uteroplacental blood flow disorder (UBFD) was recorded among all women with preterm labor. However, severe degree was found significantly more often in mothers of the 2nd group ($p_{1-2}=0,006$, $p_{1-3}=0,026$, $p_{2-3}=0,00001$), which is possibly associated with a longer course of CPI in this category. Low water level prevailed over polyhydramnios, being detected significantly more often in women who gave birth at 28-31 weeks of gestation period ($p_{1-2}=0,005$, $p_{1-3}=0,00024$, $p_{2-3}=0,0001$).

Table 3.

Features of the course of this pregnancy

Nosological form	1st group (women who gave birth to children at 22-27 weeks' gestation period, n = 46)		2nd group (women who gave birth to children at 28-31 weeks' gestation period, n = 43)		3rd group (women who gave birth to full-term babies, n = 25)		p
	abs	%	abs	%	abs	%	
The threat of termination of pregnancy	26	56,5	23	53,48	2	8	$p_{1-3,2-3}$<0,01
Preeclampsia - moderately severe	8	17,39	12	27,9	0	0	p_{1-3}=0,02 p_{2-3}=0,005
Preeclampsia - severe	6	13	5	11,62	0		
UBFD - I degree	4	8,69	8	18,6	0	0	p_{2-3}=0,026
- II degree	5	10,86	4	9,3	0	0	
- III degree	8	17,39	20	46,51	0	0	p_{1-2}=0,006 p_{1-3}=0,026 p_{2-3}=0,00001
CPI - compensated	1	2,17	2	4,65	1	4	
- subcompensated	13	28,33	19	36,58	0	0	p_{1-3}=0,003 p_{2-3}=0,0001
- decompensated	9	19,56	11	25,58	0	0	p_{1-3}=0,017 p_{2-3}=0,007
Low water level	12	26	20	46,51	0	0	p_{1-2}=0,005 p_{2-3}=0,0001 p_{1-3}=0,00024
Polyhydramnios	6	13	7	16,27	0	0	P_{2-3}=0,039
Detachment of a normally located placenta	8	17,39	5	11,62	0	0	p_{1-3}=0,026
CI	14	30,43	11	25,58	0	0	P_{2-3}=0,007 P_{1-3}=0,002
PRFB	15	26,66	6	13,95	0	0	p_{1-2}=0,024 p_{1-3}=0,001
Long latency period	9	19,56	3	6,97	0	0	p_{1-3}=0,017
Gestational diabetes mellitus	3	6,52	11	25,58	2	8	p_{2-3}=0,007
Chorioamnionitis	9	19,56	1	2,32	0	0	p_{1-2}=0,007 p_{1-3}=0,017

Note. *In connection with the identification of several pathological signs in the same woman, the total number of cases exceeds 100%, p1-2, p1-3, p2-3 - the significance of differences between groups of mothers (χ2 test with a Yates correction): 1 - mothers, those who gave birth to children at 22-27 weeks' GP, 2 - mothers who gave birth to children at 28-31 weeks' GP, 3 - a comparison group.*

Gestational diabetes mellitus, which increases the likelihood of pregnancy complications due to increased insulin secretion and decreased sensitivity to it, was diagnosed in a quarter of women in group 2 (p_{2-3} = 0.007, $p_{1-2.1-3}$≥0.05). Premature rupture of the fetal bladder (PRFB) was observed significantly more often in women who gave birth to children of gestational age of 22-27 weeks (p_{1-2} = 0.024). It was also accompanied by a long anhydrous interval of more than 12 hours, which was one of the risk factors for preterm birth. Chorioanionitis was identified significantly more often in women of the 1st group (p_{1-2} = 0.007, p_{1-3} = 0.017). Premature detachment of the normally located placenta was detected only in the main groups (p_{1-3} = 0.026, $p_{1-2.2-3}$≥0.05). Operative delivery of mothers of premature infants in the interests of the mother and the fetus by caesarean section was significantly higher compared to the comparison group (67.4% and 86% versus 60%, p_{2-3} = 0.045). The main indications for surgery were preeclampsia of moderate and severe severity, sub- and decompensation of uterine-fetal blood flow, progressive placental abruption. In the comparison group, the delivery of women in a planned manner by caesarean section was carried out according to the indications of the mother.

Thus, the antenatal period of children with ELBW proceeded against the background of the threat of termination of pregnancy, preeclampsia of moderate severity, chronic placental insufficiency, oligohydramnios, and isthmic-cervical insufficiency. Chorioamnionitis and premature rupture of the membranes were found significantly more often in women with very early preterm birth, while in women with early preterm labor - grade III UBFD, which subsequently led to a complicated course of the postnatal period of newborns. In the course of the study, it was found that the antenatal period of children with ELBW proceeded against the background of the threat of termination of pregnancy, moderate preeclampsia, chronic placental insufficiency, oligohydramnios, and isthmic-cervical insufficiency. Chorioamnionitis and premature rupture of the fetal bladder were found significantly more often in women with early preterm labor, while in women with early preterm labor - grade III UBFD, which subsequently led to the more frequent development of infectious pathology (sepsis and pneumonia - 78.6%) and death (8.7%) in the early neonatal period in newborns with GA of22-27 weeks and FGRS in children with GA of28-31 weeks (83.7%).

According to the literature, along with infectious and inflammatory pathology, the causes of death include respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), left ventricular failure and

systemic hypotension, hemodynamically relevant functioning ductus arteriosus (HRFDA) [1, 2, 3, 4, 5]. The severity of respiratory disorders in this category of children is associated with gestational age, body weight, sex of the child and the characteristics of the maternal medical history [6, 7]. The results obtained in this study also indicate that the Apgar score, severe somatic, infectious pathology and preeclampsia in mothers, which were significantly more common in women of the 1st group, were of significant importance in the severity of RDS. The mode of delivery is also a significant factor that affects the condition of the child at birth and further postnatal adaptation. Babies who later died were born via natural maternal passages, however, according to Adams M., planned cesarean section does not have any advantages over vaginal birth in this contingent of children [8]. According to N. V. Bashmakova, the best survival rate of deeply premature infants with ELBW was observed at a gestational age of more than 26 weeks, while it is preferable to use an operative method of delivery. Moreover, with a gestational age of less than 26 weeks, the mode of delivery did not affect the outcome [9].

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Chapter II. FEATURES OF THE POSTNATAL PERIOD OF PREMATURE INFANTS

2.1. Clinical aspects of perinatal complications in children with extremely low body weight

Perinatal hypoxia, together with morphofunctional immaturity, anatomical, physiological and adaptive capabilities of the body, has a pronounced effect on the course of the neonatal period and long-term prognosis of a deeply premature newborn [1]. Perinatal damaging factors and disruption of the child's adaptation to extrauterine life can disrupt the genetically determined normal development and differentiation of neurons and become a substrate for the implementation of the pathological process, especially in the periventricular zones taking into account the deep immaturity of the brain and compensation mechanisms that can protect it [2]. The lack of mechanisms for autoregulation of the vascular network in the periventricular zones directly depends on the state of systemic hemodynamics [3, 4]. In this regard, the problem of prevention of subependymal hemorrhages (SH) is especially urgent, given their frequency, high morbid and thanatogenic role [5, 6, 86]. There is an extremely thin line between the process of increasing the severity of SH and their transformation into intraventricular hemorrhages (IVH), therefore it is very important to prevent this process during the period of early neonatal adaptation of children with ELBW [7].

Due to the anatomical and physiological characteristics of the nervous system, IVHs are prevalent mainly in premature infants, the frequency and severity of IVHs is inversely proportional to gestational age. With I and II degrees of hemorrhagic lesions of the central nervous system, the prognosis is usually favorable, with IVH of III degree, up to 40% of deeply premature infants have significant impairment of cognitive functions, and almost 90% with IVH of IV degree become disabled due to severe neurological disorders [8, 9]. Due to anatomical and physiological features and lack of vascular autoregulation mechanisms, the periventricular zones of the brain of deeply premature infants are threatened by the development of hypoperfusion and tissue ischemia, the formation of periventricular leukomalacia (PVL) -polyethiological lesion of the white matter of the brain, the leading provoking factors of development of which are hypoxia/asphyxia at birth, infection (maternal chorioamnionitis, early sepsis), respiratory disorders leading to changes in blood pressure and gas homeostasis [3, 10, 11, 12, 13, 14]. PVL is diagnosed in up to 10-15% of deeply premature infants with ELBW and leads to the formation of cerebral palsy and visual impairment [9]. The development of cystic PVL, which is white matter gliosis in the brain, is the most unfavorable in terms of long-term neurological prognosis i.e. a high risk of severe retardation of psychomotor development, neurosensory disorders, cerebral palsy (CP), epilepsy [3, 15].

In the literature, data are indicated on the relationship between the development of PVL and the severity of respiratory disorders, for example, deeply premature infants who retained spontaneous breathing from birth developed PVL in 6% of cases, while newborns unable to breathe on their own developed PVL in 60%. The incidence of PVL in children born at the time of early preterm birth who died after the end of the early neonatal period was 75%, while in surviving children it was 4-10% [3]. According to N. V. Bashmakova and co-authors, infectious pathology is in third place in the structure of morbidity in children with ELBW [15]. According to the literature data of national authors, the most significant infections (intrauterine generalized infections, bacterial sepsis, pneumonia, generalized candidiasis, necrotizing enterocolitis) occupy a leading place in the causes of mortality in deeply premature infants and are defined as the most important prognostic factor in relation to unfavorable delayed results [16, 17]. The predisposition of children with ELBW to a generalized infectious process is due to the failure of the immune system, immaturity of skin and epithelial barriers, and a high frequency of invasive manipulations [18].

The mortality rate of deeply premature infants with infectious pathology reaches 25-65%, significantly (5-10 times) higher than the level in full-term newborns [19]. In recent years, the issue of the nosocomial nature of infectious pathology in children with ELBW who survived the early neonatal period and are in the NICU for a long time has been actively discussed [20].

The most significant cause of infectious pathology of the perinatal period of deeply premature infants is intrauterine infection (UI) [21], which is characterized by placentitis, leading to chronic placental insufficiency and the birth of premature infants [22]. Difficulty in the diagnosis of the infectious process is associated with the complexity of interpretation or the absence of a number of clinical symptoms and laboratory parameters in newborns with ELBW due to a protracted course that mimics RDS in the first days of life, CNS damage, especially with aggravation of FGRS, IVH, malformations, extreme immaturity [8, 23]. Modern therapeutic and prophylactic approaches aimed at reducing the incidence of infectious pathology in this category of children are not effective enough [24], and the clinical and diagnostic aspects of sepsis are constantly being revised [25, 26, 27]. To make a diagnosis of sepsis, it is necessary to isolate the systemic inflammatory response syndrome with multiple organ failure [28].

Neonatal sepsis is a risk factor for delayed neurological complications and a leading cause of mortality, accounting for 25 to 45% according to the authors [29, 30, 31, 32]. At the same time, overdiagnosis of bacterial infection in deeply premature infants leads to the unjustified prescription of antibiotic therapy and polypharmacy. The authors argue that long-term routine prophylactic antibiotic therapy and administration of immunoglobulins with negative results of blood culture does not reduce the risk of developing an infectious process (pneumonia and sepsis) in children with ELBW [33] and can cause serious complications, increasing the risk of developing necrotizing enterocolitis (NEC) and death [34].

In recent years, the number of children with hemodynamically relevant functioning ductus arteriosus (HRFDA) has been increasing, and the number of cases of clinically pronounced functioning ductus arteriosus is inversely proportional to gestational age. Long-term preservation of HRFDA is observed mainly in children with ELBW, who were born at the time of very early preterm birth. HRFDA negatively affects lung tissue, is a risk factor for the formation of NEC, IVH and hypoxic lesions of the central nervous system [35]. On the background of HRFDA during the adaptation period in premature newborns, transient persistent pulmonary hypertension (PPH) can be observed, which occurs according to M. V. Fomichev (2006) in 15-35% [36]. The process develops after long-term oxygen therapy due to spasm and hyperplasia of the muscular sheath of small pulmonary arteries, which leads to a pronounced increase in vascular resistance [35, 36]. Treatment of HRFDA is carried out with cycooxygenase inhibitors, the effectiveness of which reaches 75-80% with early application [37].

One of the reasons that worsen the quality of life of children with ELBW is anemia of prematurity, which develops due to an increase in the volume of circulating blood against the background of the rapid growth of the child, incommensurate with the rate of erythropoiesis, a short life span of fetal erythrocytes, low production of erythropoietin. Therefore, repeated blood transfusions are concomitant component of therapy [38. 39]. Anemias develop the more often, the shorter the gestational age and the baby's body weight at birth. Term infants, in contrast to infants with ELBW, are capable of responding with rapid production of erythropoietin to hypoxia [38].

According to the literature, in the structure of neonatal morbidity in deeply premature infants, there is a combined pathology. The first places are traditionally occupied by respiratory distress syndrome (RDS), hypoxia and asphyxia. Infectious pathology in the structure of morbidity is in third place [40].

Respiratory distress syndrome (RDS) in newborns with ELBW is the most common cause of respiratory distress, often leading to death [9, 41]. Rates of neonatal mortality from RDS range from 20 to 95% [42]. The severity of respiratory disorders in this category of children is associated with gestational age, body weight, sex of the child and the characteristics of the maternal history [43, 44, 45]. The reason for the development of RDS is surfactant deficiency and morphological immaturity of the lung tissue. The synthesis of surfactant begins at the 26th week of gestation, therefore, the incidence of RDS is inversely proportional to the gestational age and body weight at birth. According to Russian authors, RDS develops in 78–88% with gestational age up to 28 weeks, 70% - up to 29–30 weeks, 50–55% - up to 31–32 weeks [42]. Previously, the main method of treatment of respiratory disorders in RDS was artificial lung ventilation (ALV) [46]. To date, there are several approaches to the use of surfactant drugs, the leading role, undoubtedly, is given to preventive therapy [42]. The advantages of early prophylactic surfactant administration in the delivery room versus delayed admin-

istration in the intensive care unit of newborns is a reduction in neurological complications, bronchopulmonary dysplasia, necrotizing enterocolitis, and mortality in premature infants. There is evidence in the literature that early administration of a surfactant and the use of respiratory support by the CPAP method after birth in children with ELBW with respiratory disorders reduces the length of stay of children in intensive care units for newborns and early rehabilitation [42]. Despite the improvement of life-saving treatment methods, it is not possible to completely prevent the most severe complication of RDS i.e. bronchopulmonary dysplasia (BPD), which has a great impact on the prognosis of the health of children with ELBW, and in severe cases, life [9].

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2.2. Clinical features of children with extremely low birth weight

Our study involved 89 children with ELBW of gestation at 22-31 weeks gestational age who were nursed at the Department of Early Neonatal Rehabilitation and 25 healthy preterm infants.

In the course of the study, all deeply premature infants with ELBW, depending on the gestational age at birth (body weight less than 1000 g at birth), were divided into two main groups with respect to 28 weeks - gestational age, which is the "zone of extreme immaturity" for newborns, according to ICD- X. The maturity of a newborn child is the most important indicator of intrauterine development, which is determined by the totality of clinical, morphological, biochemical and functional signs specific to a given gestational age of the child.

The distribution of children into groups by birth weight, namely from 500 to 749 grams ("zone of the viability limit", gestation period 22-26 weeks) [176]

and from 750 to 999 grams, we considered incorrect due to the high percentage of perinatal losses in the 1st group (39.1% versus 12.6% of children) [16] and the presence of survivors in the 1st group of children weighing from 500 to 749 g with fetal growth retardation syndrome (FGRS), born at an early stage premature birth.

Thus, with this in mind, premature infants were divided into two main groups:

Group 1 - 46 infants with ELBW, born at a gestational age of 22-27 weeks;

Group 2 - 43 infants with ELBW, born at a gestational age of 28-31 weeks.

Group 3 - a comparison group - 25 full-term healthy newborns born to conditionally healthy women of favorable reproductive age (20-34 years) with physiological pregnancy, childbirth and the postpartum period. The children of the comparison group having been breastfed from the moment of birth, had a physiological neonatal period and were discharged at the age of 4-5 days of life in a satisfactory condition.

Clinical observation and immunological studies were carried out from the moment of birth and after reaching the postconceptinal age (37-40 weeks).

Analysis of the clinical condition showed that all premature infants were born with low scores on the Apgar scale, which reflects the severity of asphyxia and intrauterine suffering. In children with GA of22-27 weeks in the first minute, severe asphyxia was more often detected (less than 3 points on the Apgar scale) in 26.19% of cases versus 16.27% (p_{1-2}> 0.05) children with GA of28- 31 weeks (Table 4).

Table 4.

Assessment on the Apgar scale in children with ELBW (M ±σ)

Indicators	1st group (n=46)	2nd group (n=43)	3rd group (n=25)	p
1st minute, points	4,16±1,03	4,38±1,45	6,83±1,57	**p_{1-3}≤0,001** **p_{2-3}≤0,001**
5th minute, points	5,83±0,72	6,27±0,72	7,66±1,68	p_{1-2}=0,006 **p_{1-3}≤0,001** **p_{2-3}≤0,001**

Note: *p1-2, p1-3, p2-3 - significance of differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

30 (65.21%) and 23 (53.49%) premature infants (4-5 points on the Apgar scale at the 1st minute of life, p_{1-2}> 0.05) had signs of a moderate degree of asphyxia. All full-term babies were born without signs of asphyxia.

Asphyxia is a state of disturbance of gas homeostasis, accompanied by hypercapnia, hypoxemia and metabolic (or mixed) acidosis [1]. Until the mid-80s of the last century, the main criterion for the severity of newborn asphyxia was

the assessment according to the Apgar scale of the International Classification of Diseases (IX revision 1975), (rubrics 768, 768.5; 768.6). A number of authors believe that the Apgar scale is less informative in predicting hypoxic brain damage in newborns than pH and base deficiency (BE), and the dynamics of neurological complications is most important [2, 3]. Metabolic acidosis more adequately reflects the severity and duration of perinatal hypoxemia. The BE indicator is more informative in comparison with pH, since it is not affected by respiratory acidosis, and it correlates with metabolic acidosis [4].

When assessing the parameters of the electrolyte and acid-base composition of blood in premature newborns of the 1st group in the first hours of life, a statistically significant decrease in the level of sodium and partial oxygen tension was revealed in comparison with the newborns of the 2nd group (Table 5).

Table 5.

Indicators of the acid-base balance of children with ELBW at birth (M±

Indicators	**Gestational age 24-27 weeks (1st group n = 46)**	**Gestational age 28-31 weeks (2nd group, n = 43)**	**Full-term babies (3rd group, n = 25)**	**p**
pH	7,33±0,067	7,35±0,07	7,3±0,09	
pCO_2, mm Hg	37,14±8,15	39,7±11,49	46,47±9,49	**p_{1-3}=0,0001 p_{2-3}=0,015**
pO_2, mm Hg	51,73±9,31	57,2±13,12	22,5±9,41	**p_{1-2}=0,028 p_{1-3}=0,001 p_{2-3}=0,001**
cHCO3, mmol/L	19,85±3,76	21,46±4,03	20,2±3,22	**p_{1-2}=0,05**
BEecf, mmol/L	-4,99±4,14	-3,42±3,83	-4,06±3,58	
$_cK^+$, mmol/L	9,15±3,36	10,07±8,65	4,67±0,68	**p_{1-3}=0,0001 p_{2-3}=0,0001**
$_cNa^+$, mmol/L	126,33±6,97	129±5,56	135,17±2,98	**p_{1-2}=0,05 p_{1-3}=0,0001 p_{2-3}=0,0001**
$_cCa^{2+}$, mmol/L	1,13±0,11	1,17±0,15	0,99±0,38	**p_{1-3}=0,027 p_{2-3}=0,007**

Note: *p1-2 - significance of differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The deficiency of buffer bases in infants with a younger gestational age was more pronounced (p_{1-2} = 0.07) than in children of gestational age 28-31 weeks.

Premature infants of both groups were characterized by hyponatremia (p_{1-2} = 0.05) against the background of hyperkalemia, which indicates the extreme immaturity of the excretory system of children due to insufficient maturation of the kidney pores [5].

In the 1st group of children in the acid-base balance, metabolic acidosis was the leading disorder. This disorder was noted in 23.91% of cases, in the remaining children with ELBW, changes were diagnosed in the form of mixed acidosis (19.56%), respiratory acidosis (4.34%) and respiratory alkalosis (2.17%).

In group 2, metabolic acidosis also dominated in 27.9% of cases, mixed and respiratory acidosis was noted somewhat less frequently (18.6% and 23.26%).

The average gestational age of children born at the time of very early preterm birth significantly differed from the same indicator for children of the 2nd and 3rd groups (Table 6) (p <0.001 in all cases).

Table 6.

Anthropometric data of children with ELBW (M ±σ)

Indicators	1st group (n=46)	2nd group (n=43)	3rd group (n=25)	p
Gestational age, weeks	25,89±1,26	29,13±1,32	39,32±0,8	**p_{1-2}≤0,001 p_{1-3}≤0,001 p_{2-3}≤0,001**
weight, g	822,15±125,74	892,47±111,8	3451,87±470,72	**p_{1-2}=0,006 p_{1-3}≤0,001 p_{2-3}≤0,001**
length, cm	33,38±4,16	33,62±2,7	51,16±2,83	**p_{1-3}≤0,001 p_{2-3}≤0,001**
head circumference, cm	24,25±1,93	25,63±2	34,83±1,63	**p_{1-2}=0,004 p_{1-3}≤0,001 p_{2-3}≤0,001**
chest circumference, cm	21,77±2,07	24,22±2,19	34,33±1,65	**p_{1-2}=0,001 p_{1-3}≤0,001 p_{2-3}≤0,001**

Note: *p1-2, p1-3, p2-3 - significant differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

By gender, the main groups were comparable.

Anthropometric indicators of premature newborns, with the exception of body length, also significantly differed (p <0.001 in all cases).

Thus, children from very early preterm births had lower anthropometric data at birth, which is associated with a lower gestational age (22-27 weeks). All premature infants were born in a state of asphyxia, which is confirmed by low Apgar scores and metabolic acidosis based on the results of the study of gas homeostasis.

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2.3. Features of the course of the postnatal period in children with extremely low body weight

According to our data, fetal growth retardation syndrome (FGRS) in children born from early preterm birth was recorded much more often than in children with gestational age of 22-27 weeks (p_{1-2} = 0.0001) (Table 7), which associated with UBFD and clinical manifestations of chronic renal failure.

Table 7.

Degree of incidence of FGRS in children with ELBW

Indicators	1st group (n=46)		2nd group (n=43)		
	abs	%	abs	%	
IGRS, total	8	17,4	36	83,7	**p_{1-2}=0,0001**
IGRS hypoplastic option	6	13,04	27	62,79	**$p_{1-2=}$0,0002**
IGRS hypotrophic variant	2	4,34	9	20,93	**p_{1-2}=0,02**

Note: *p1-2, p1-3 p2-3 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

At the same time, hypoplastic (small fetal size for GA according to ICD X) and hypotrophic ("low weight" fetus for GA according to ICD X) variants of FGRS prevailed 4.5 times more often in children born at 28-31 weeks of GA.

From the operating and delivery unit, all deeply premature infants with ELBW in serious condition were transferred to the intensive care unit and neonatal intensive care unit (NICU) to create optimal conditions for nursing. All premature infants received enteral feeding from the first day of life, children of the 2nd group in a greater percentage of cases were fed with breast milk (79% versus 47.83%, $p_{1-2} = 0.015$).

Early neonatal mortality among children born at the very early preterm birth was 8.7% (4 children).

Infectious diseases (early neonatal sepsis), confirmed by laboratory data (high level of C-reactive protein, positive blood culture), were in the lead in the structure of the causes of death in children with GA of22-27 weeks. When analyzing the identified pathogens of blood culture, gram-negative flora prevailed i.e. in 75% of cases *Klebsiella* and *E. coli* were found, in 25% of cases - *Staphylococcus haemolyticus*.

With the stabilization of vital functions, effective spontaneous breathing, most children with ELBW (1st group - 93.48%, 2nd group - 100%) at the age of 1 month of life were transferred to the neonatal pathology department to continue nursing and treatment (Table. 8).

Table 8.

Average duration of respiratory therapy, ICU stay and NPU

Indicators	1st group (n=42)	2nd group (n=43)	p
IVL, day	11,61±10,77	2,93±4,34	**p_{1-2}=0,0001**
CPAP, day	4,52±4,32	3±2,53	**p_{1-2}=0,05**
NICU, day	19,78±12,83	8,9±5,76	**p_{1-2}=0,0001**
NPU, day	54,63±12,61	55,94±16,15	
Length of hospital stay, day	75,75±19	64,74±17,13	

Note: *p1-2 - significance of differences between groups of children (Student's criterion): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

Combined pathology was noted in the morbidity structure of very premature infants with ELBW. 100% of premature infants suffered from RDS of various degree of severity. However, mechanical ventilation was required for 89.1% and 58.1% of newborns in groups 1 and 2 (Table 9).

The need for long-term mechanical ventilation in children of group 1 was significantly higher than in children of group 2, which was due to the severity of the condition and greater immaturity of the alveoli (p_{1-2} = 0.0001). Term infants had no neurological and somatic pathology, they were discharged in satisfactory condition, breastfed on 3-5 days of life.

Table 9.

The structure of morbidity in children with ELBW at the age of 1 month of life

Nosological form	1st group (n=42)		2nd group (n=43)		p
	abs	%	abs	%	
RDS	42	100	43	100	
Hypoxic-ischemic CNS damage: cerebral ischemia II degree	0	0	5	11,63	
cerebral ischemia III degree	42	100	38	88,37	
Ischemic-hemorrhagic lesions of the CNS: IVH I degree	7	16,7	8	18,6	
IVH II degree	11	26,19	2	4,65	**p_{1-2}=0,02**
IVH III degree	8	19,04	2	4,65	**p_{1-2} =0,023**
Pneumothorax	5	11,9	0	0	$p_{1-2=}$0,019
BPD	17	40,48	3	6,98	**p_{1-2}=0,0001**
Sepsis	15	35,71	3	6,98	**p_{1-2}=0,001**
Pneumonia	27	64,29	10	23,26	**p_{1-2}=0,0001**
Meningitis	2	4,76	0	0	
Cytomegalovirus infection	4	9,52	1	2,32	
HRFDA	6	14,28	1	2,32	**p_{1-3}=0,024**
Anemia -severe severity	22	52,38	12	27,9	p_{1-2}=0,017

Note: *due to the detection of several pathological signs in the same child, the total number of observations does not correspond to 100%. p1-2 is the significance of differences between groups of children (χ2 criterion with Yates' correction): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

Most children with ELBW were diagnosed with hypoxic-ischemic damage to the central nervous system of severe severity, cerebral ischemia of the II degree in children with GA of 28-31 weeks did not exceed 12% of cases. According to the

"Classification of Perinatal Nervous System Affections in Newborns" (2005), the severity of CNS affections was determined by the presence of neonatal seizures, the duration of the depression syndrome, and the dynamics of structural changes in the brain according to NSG [1].

In children of gestational age of 22-27 weeks, severe forms of intraventricular hemorrhage (IVH) were significantly more frequent. So, II degree of IVH was diagnosed 5.63 times ($p_{1-2} = 0.02$), and III degree 4 times more often than in children of the 2nd group ($p_{1-2} = 0.023$), which is primarily due to good blood supply to the germinal matrix, the vessels of which have wide lumens without muscle fibers and basement membrane, which contributes to high vulnerability.

Due to the increased susceptibility of premature infants to infectious agents, there was a high frequency of infectious and inflammatory pathology, more characteristic of children of gestational age of 22-27 weeks, so pneumonia and sepsis were diagnosed reliably more often than in children of the 2nd group ($p_{1-2} = 0.0001$). Intrauterine sepsis of staphylococcal etiology in children of the 1st group occurred 4 times more often than in children of gestational age of 28-31 weeks (19.04% and 4.65%, $p = 0.023$). Early neonatal pneumonia was diagnosed in 23.8% of cases in newborns of the 1st group and in 13.95% of cases in newborns of the 2nd group. There were no significant differences in the incidence of cytomegalovirus infection (CMVI) and meningitis. Congenital cytomegalovirus infection was diagnosed in 4.76% and 2.32% of cases of children with ELBW. Anemia of severe prematurity was more often diagnosed in children of the 1st group ($p_{1-2} = 0.017$), which is associated with factors of incomplete ontogenesis, and can also be one of the manifestations of infection and potentiate its postnatal development. Bronchopulmonary dysplasia by the age of 1 month of life was diagnosed in children of the 1st group significantly more often (26.19% versus 2.32%), which was associated with a greater immaturity of the alveoli and the need for prolonged mechanical ventilation.

Patent ductus arteriosus was diagnosed reliably more often in children born at the time of very early preterm labor ($p_{1-2} = 0.024$), which is consistent with the authors' data [2].

By the age of one month, more than half of premature infants of GA of 28-31 weeks remained breastfed, with the addition of a breast milk fortifier (65.12%), in contrast to children of the 1st group (42.85%, $p_{1-2} > 0.05$), weight gain from the moment of birth of children of both groups did not differ significantly.

When analyzing the acid-base balance of premature infants at 1 month of age, no significant differences were found, with the exception of persistent hyponatremia, which was more pronounced for the 1st group ($p_{1-2} = 0.0095$) (Table 10).

Table 10

Indicators of acid-base balance in children with ELBW at the age of 1 month of life (M±σ)

Indicators	1st group (n=42)	2nd group (n=43)	p
pH	7,36±0,04	7,36±0,04	
pCO_2, mm Hg.	46,62±6,55	44,91±5,37	
pO_2, mm Hg.	44,67±7,7	48,61±10,45	
cHCO3, mmol/l	25,65±3,06	25,13±3,9	
BEecf, mmol/l	0,71±3	0,22±3,73	
$_cK^+$, mmol/l	5,68±0,87	5,38±1,18	
$_cNa^+$, mmol/l	130,65±2,96	132,5±2,86	**p_{1-2}=0,0095**
$_cCa^{2+}$, mmol/l	1,32±0,07	1,32±0,06	

Note: *p1-2 - significance of differences between groups of children (Student's criterion): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

In the 1st group of children, the dominant disorder in the acid-base balance at 1 month of life was respiratory acidosis, which was noted in 33.33% of cases, in 2.38% of children, disorders in the form of metabolic acidosis were noted.

In 2nd group, respiratory acidosis also dominated in 25.58% of cases, metabolic acidosis was noted somewhat less frequently (4.65%).

Children with a shorter gestation period spent a longer time in the ICU on ALV, which led to a later transfer to the stage of early rehabilitation. By the age of 1 month, very premature babies had associated pathology. In children of the 1st group, IVH of II, III degree were significantly more often diagnosed, anemia of severe severity requiring blood transfusions, a higher frequency of infectious and inflammatory pathology (pneumonia, sepsis) was revealed. A higher incidence of BPD in this category of children was associated with prolonged exposure to mechanical ventilation and was accompanied by respiratory acidosis due to gas homeostasis.

Upon reaching PCA 38-40 weeks, both groups had concomitant pathology (Table 11).

Table 11.

The morbidity patterns in children with ELBW to PCA 38-40 weeks

Nosological form	1st group (n=42)		2nd group (n=43)		p
	abs	%	abs	%	
RDS	0	0	5	11,63	
Hypoxic-ischemic CNS damage: cerebral ischemia II degree	42	100	38	88,37	
cerebral ischemia III degree	27	64,3	16	37,2	**p_{1-2}=0,03**
Ischemic-hemorrhagic lesions of the CNS: IVH I degree	8	19,04	11	25,58	
IVH II degree	11	26,19	2	4,65	**p_{1-2}=0,001**
IVH III degree	8	19,04	3	6,98	**p_{1-2}=0,042**
BPD - moderately severe	12	28,57	6	13,95	
-severe	11	26,19	6	13,95	p_{1-2}=0,056
Pneumonia	27	64,29	10	23,26	**p_{1-2}=0,0001**
Cytomegalovirus infection	6	14,28	4	9,3	
PH I degree	5	11,9	12	27,9	**p_{1-2}=0,04**
II degree	21	50	24	55,8	
III degree	16	38	7	16,27	**p_{1-2}=0,039**
Hernia - umbilical	1	2,38	3	6,97	
- inguinal	10	23,8	14	32,55	
Anemia severe	42	100	40	93	

Note: *due to the identification of several pathological signs in the same child, the total number of observations does not correspond to 100%, p1-2, p1-3, p2-3 - the significance of differences between groups of children (χ2 criterion with Yates' correction): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

After past RDS in case of clinical and radiological examination, moderate and severe bronchopulmonary dysplasia was diagnosed more often in children of group 1 (p_{1-2}> 0.05), which is consistent with the authors' data [3]. The classical form of BPD prevailed over the “new” one and was found significantly more often in children of the 1st group (50% versus 34.9%, p_{1-2} = 0.013).

The frequency of intraventricular hemorrhages of varying severity remained higher in children of the first group (p = 0.03). During the time of being at the stage of early rehabilitation, the number of IVH of the 1st degree among children with ELBW increased to 19.04% and 25.58%. Occlusive hydrocephalus was diagnosed in two children with GA of22-27 weeks with IVH degree III, requiring surgical intervention (4.76%).

In the clinical picture of CNS damage in very premature infants with ELBW, the syndrome of motor disorders of the type of lower spastic paraparesis was the leader in 26.19% and 44.19% of children with GA of22-27 and 28-31 weeks (p_{1-3} = 0.0003, p_{2-3} = 0.00007). Spastic tetraparesis was observed in premature infants of the 1st group in 11.9% of cases, the 2nd - in 2.32%. Hypertensive-hydrocephalic syndrome was detected in 80.1% and 65.11% of children in the main groups. Bulbar disorders and convulsive syndrome were diagnosed only in children born at the time of very early preterm birth, in 7.14% of cases.

The frequency of infectious and inflammatory pathology (pneumonia) also remained at a high level in children of gestational age of 22-27 weeks (p_{1-2} = 0.0001). By the post-conceptual age of 38-40 weeks, the detection rate of cytomegalovirus infection in children of both groups increased by 1.5 and 4 times, which is possibly associated with repeated blood transfusions.

All children of the main groups were diagnosed with premature anemia. However, the number of blood transfusions performed was significantly higher in children of gestational age 22-27 weeks (2.59 ± 1.99 versus 1.49 ± 1.4 times, p_{1-2} = 0.008).

Significant differences were found in the incidence of retinopathy, which is characteristic only of preterm infants, the severity of which is inversely proportional to the gestational age of the child [4]. The incidence of retinopathy degree II in the groups was comparable, while retinopathy degree III occurred 2.6 times more often in children born at the time of very early preterm labor (p_{1-2} = 0.039), for which the children underwent repeated laser coagulation of the avascular zones retina. PH V degree was not detected in any child.

Inguinal hernias in children of both groups were more common than umbilical hernias, however, there were no significant differences in the frequency of hernias.

By PCV 38-40 weeks, the number of children exclusively breastfed with the addition of the fortifier decreased 3.42 and 1.23 times (up to 19.05% and 34.88%) of children of both groups (p_{1-2}> 0, 05) (Table 12).

Table 12.

Feeding patterns of children with ELBW

Indicators	1st group (n=42)	2nd group (n=43)	p
Early neonatal period			
Breast-feeding, %	47,83	79	p_{1-2}=0,015
Artificial feeding, %	52,17	21	p_{1-2}=0,008
1 month of life			
Breast-feeding, %	42,85	65,12	
Artificial feeding, %	35,71	20,93	p_{1-2}=0,04
Mixed feeding, %	21,44	13,95	
PCA 38-40 weeks			
Breast-feeding, %	19	34,88	
Artificial feeding, %	35,71	27,9	
Mixed feeding, %	45,29	37,22	

Note: *p1-2 - the significance of differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

When assessing the body weight of premature infants in the dynamics of the postnatal period after reaching the postconceptional age of 38-40 weeks, significant differences were revealed (Table 13).

Table 13.

Dynamics of changes in body weight of very premature infants (M ±σ)

Indicators	1st group (n=42)	2nd group (n=43)	p
At the age of 1 month			
Weight, g gain since birth, g gain since birth,%	1149,57±195,2 295,65±124,82 34,4±13,05	1226±236,43 330,07±168,93 36,39±16,99	**p_{1-2}=0,006**
At the age of 38-40 weeks			
Weight, g gain since birth, g gain since birth,%	2159±213,29 1288,24±264,13 156,22±46,35	2008,05±185,58 1177,41±264,44 126,83±41,7	**p_{1-2}=0,002** p_{1-2}=0,08 **p_{1-2}=0,007**

Note: *p1-2 - the significance of differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

At birth, the body weight of children born at the time of very early preterm birth was significantly lower (p_{1-2} = 0.006), by the age of 1 month, the weight

gain of children of the 2nd group exceeded the indicators of children with a shorter gestation period. However, upon reaching the age of a full-term newborn, children of the 1st group had higher body mass indices ($p_{1-2} = 0.002$).

When the PCA reached 38-40 weeks, when studying the indicators of the acid-base balance, no significant differences were found (Table 14). The calcium level of children of gestational age 22-27.6 weeks was decreased at the level of the trend. According to some authors, in premature infants, the system that maintains a sufficient level of blood calcium is formed later, which creates special difficulties for them in phosphate-calcium homeostasis [5].

In both groups of premature infants, the dominant disorder in the acid-base balance was respiratory acidosis (11.9% and 6.98% of cases), which correlates in children with severe BPD.

Table 14.

Indicators of acid-base balance in children with ELBW at 38-40 weeks of PCA (M±σ)

Indicators	1st group (n=42)	2nd group (n=43)	P
pH	7,37±0,03	7,37±0,04	
pCO_2, mm Hg.	46,5±7,22	45,17±5,11	
pO_2, mm Hg.	47,25±6,35	46,29±7,7	
cHCO3, mmol/l	26,65±5,07	25,66±2,24	
BEecf, mmol/l	1,73±5,02	0,97±2,2	
$_cK^+$, mmol/l	5,63±1,6	5,27±1,03	
$_cNa^+$, mmol/l	134,77±5,52	133,84±3	
$_cCa^{2+}$, mmol/l	1,31±0,13	1,37±0,09	**p_{1-2}=0,051**

Note: *p1-2 - the significance of differences between groups of children (Student's test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

During the nursing period, all premature infants received antibiotic therapy, the duration of which was longer in the 1st group of children (43.19 ± 12.95 versus 28.79 ± 8.76 days, p = 0.0004), which is associated with more a high frequency of infectious and inflammatory pathology and a long stay in a hospital.

The frequency of use of immunobiological drugs, such as "Pentaglobin", was comparable in both groups (2.43 ± 1.88 and 2.39 ± 1.86 times, p <0.05). All premature infants diagnosed with CMV disease were treated by intravenous administration of "Neocytotect" and "Virolex" as prescribed by an Infectious Disease Physician.

Upon reaching PCA 38-40 weeks, children born in the term of very early pre-

term birth had a more complicated somatic pathology: a high level of ischemic-hemorrhagic affection of the central nervous system and bronchopulmonary dysplasia of severe severity, threshold retinopathy and infectious and inflammatory pathology (pneumonia) remained.

Thus, the postnatal period of deeply premature infants with ELBW was characterized by severe concomitant pathology.

Considering the deep immaturity of the brain and compensation mechanisms that can protect it, perinatal damaging factors and disruption of the child's adaptation to extrauterine life disrupt the genetically determined normal development and differentiation of neurons and become fertile ground for the implementation of the pathological process, especially in the periventricular zones [6]. All very premature infants were diagnosed with hypoxic-ischemic affection of the central nervous system against the background of postponed asphyxia at birth in the early neonatal period. Severe brain damage was more often detected in newborns with GA of22-27 weeks, in which subsequently severe IVH was diagnosed reliably more often due to the lack of mechanisms of autoregulation of the vascular network of the periventricular zones, which is consistent with the data of domestic and foreign authors [7, 8].

Due to anatomical and physiological features and the absence of vascular autoregulation mechanisms, the periventricular zones of the brain of deeply premature infants are threatened by the development of hypoperfusion and tissue ischemia, the formation of periventricular leukomalacia (PVL), the leading provoking factors of the development of which are severe hypoxia / asphyxia at birth, infection (chorioamnionitis in the mother, early sepsis), respiratory disorders leading to changes in blood pressure [7, 9, 10, 11]. PVL is formed in 10-15% of very premature infants with ELBW and causes the development of cerebral palsy and visual impairment [12]. The syndrome of movement disorders of the type of lower spastic paraparesis in every fourth and second child of the 1st and 2nd groups, respectively, however, spastic tetraparesis was observed in premature infants of gestational age 22-27 weeks 5 times more often.

Despite the improvement in the methods of resuscitation care, more than half of premature infants by the post-conceptual age of 38-40 weeks were diagnosed with BPD of of various degree of severity (85.71% and 58.14% among the 1st and 2nd groups). Every fifth child who developed BPD suffered from sepsis in the early period of adaptation and every second child in the neonatal period suffered from pneumonia. Sepsis was diagnosed 5.5 times more often in children with GA of22-27 weeks.

Severe forms of the disease in children with GA of22-27 weeks occurred 1.8 times more often, which is undoubtedly associated with a significantly longer stay on mechanical ventilation against the background of incomplete processes of alveolo- and angiogenesis, aggravated somatic and obstetric history of the mother (chorioamnionitis, preeclampsia), extensive intraventricular hemorrhages, functioning patent ductus arteriosus, which is consistent with the authors' data [13, 14, 15, 16, 17].

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Chapter III. CHARACTERISTICS OF CONNECTED AND ADAPTIVE IMMUNITY OF CHILDREN WITH EXTREMELY LOW BODY WEIGHT OF DIFFERENT GESTIONAL AGE

3.1. Formation of adaptive and innate immunity in children with extremely low body weight in the dynamics of the postnatal period

The immune system is one of the most unique body systems with the ability to respond quickly to various pathogens and regulate the functions of homeostasis systems during pathological processes, which determines the survival of a premature infant, the features of the postnatal period of life, the effectiveness of therapeutic and rehabilitation measures.

At the moment, the individual links of the immune system in premature newborns with various pathological conditions have been described in detail. At the same time, there are very few sources containing information on the relationship between innate and adaptive immunity in children with ELBW in the dynamics of the postnatal period, which does not allow adequately assessing the coherence of immune processes and forming an idea of various mechanisms of immunological response in very premature infants.

The maturity of the morphological substrate of the immune system of very premature infants with ELBW at the time of birth depends on the child's hepatitis B, antigen load, pathological influences, which the fetus is exposed to in the antenatal period during complicated pregnancy, as well as the violation of the relationship of immunity in the mother - fetus - newborn system [1, 2].

According to the literature, in very premature infants, the rate of maturation of the immune system differs from that in full-term infants. In contrast to full-term newborns, in children with gestational age less than 32 weeks, immunocompetent cells are immature, similar to fetal cells. Therefore, during the period of massive antigen load after birth, they are not able to provide efficiently adequate protection for the child [3]. This state of immunity in premature infants prevents the formation of overreaction processes at a high antigen load in the intra- and neonatal periods, and the mechanisms of the innate immunity link prevent the development of infection at the earliest stages as a result of the elimination of pathogens.

Adaptive immunity is realized by lymphocytes, and it can also be divided into two components (links): humoral and cellular. The basis for the development of infectious and inflammatory pathology is the immaturity of the innate and adaptive links of immunity both at the systemic and local levels [4, 5, 6]. Humoral immunity is realized by B-lymphocytes and immunoglobulins produced by them. When meeting an antigen and recognizing it, B-lymphocytes are transformed into plasma cells that synthesize antibodies. Antibodies provide protection against bacteria, bacterial toxins, viruses that circulate freely in body fluids before entering cells.

The cellular link of the adaptive immunity of deeply premature newborns is characterized by an increased number of "naive" T-lymphocytes [7], which, in comparison with mature T-cells, when interacting with antigens, produce a smaller amount of gamma-interferon and other cytokines. In addition, the interaction of T and B lymphocytes is difficult in the course of the immune response and there is a reduced number of cells of immunological memory [4, 8]. According to E. L. Semikina (2008), an analysis of the expression of the main antigens of T-linear differentiation in very premature infants indicates a sufficient maturity of this system by the time of birth. The researchers noted an increase in the level of cells with the phenotype CD3 +, CD4 +, CD8 + and the prevalence of cells with a low specificity of their antigen-recognizing immunoglobulin receptors in the total pool of B-lymphocytes [9]. Evaluation of the cellular component of immunity in very premature infants with ELBW at birth showed a decrease in the relative number of T cells, CD4 + lymphocytes, the ratio of CD4 / CD8 populations, and an increase in the number of natural killer cells (NK) in umbilical cord blood [10].

A number of studies have shown that by the end of the neonatal period in children with ELBW, compared with full-term newborns, leukocytopenia and relative lymphocytosis persist. The decrease in the relative content of CD3 + and CD4 + - lymphocytes and the value of the immunoregulatory index is due to the suppressive direction of cellular reactions. The reduced amount of serum immunoglobulins is compensated by the increased content of B-lymphocytes. An increase in the number of NK cells characterizes a high cytotoxic potential and, in conditions of a decrease in the number of neutrophils, is one of the only factors of antigen-independent cell defense [7, 11].

The CD95 receptor transmits a cytotoxic signal when it binds to specific antibodies. The CD95 receptor plays an important role in the physiology of apoptosis: the peripheral removal of activated mature T cells in the final stages of the immune response.

The receptor for IL-2, CD25, is produced by T cells in response to antigenic and mitogenic stimulation. The cytokine IL-2 is required for the proliferation of the T-cell link and other processes that regulate the immune response. The CD71 receptor appears on leukocytes upon activation. It is found on most dividing cells. As a transferrin receptor, CD71 allows the entry of iron ions into the activated cell, which is necessary for cell division. There is evidence that CD71 + cells can have an anti-inflammatory effect in the postnatal period of a newborn's life [12]. These markers of leukocyte subpopulations serve as indicators of the competence of the cellular link of the newborn's immune system. The key point is the formation of the antigen-presenting function, when different populations of cells interact to protect the body from the action of the antigen.

When analyzing the immunological parameters of umbilical cord blood in all very premature infants with ELBW, a significant decrease in the number of leukocytes was recorded ($p_{1-3} = 0.06$, $p_{2-3} = 0.007$) in combination with an increase in the percentage of lymphocytes ($p_{1-3.2-3} = 0, 0001$) compared to term infants. The

most pronounced changes were observed in children born at the time of very early preterm labor, which is associated with the peculiarity of early ontogenesis and defective leukopoiesis against the background of the pathological course of the antenatal period (Table 15).

Table 15.

Population and subpopulation composition of umbilical cord blood lymphocytes in children with ELBW

Indicators	1st group (n=46)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
Leukocytes, 10^9/l	6,15 (4,42-10,71)	6,28 (4,7-10,62)	10,85 (9-14,5)	**p_{1-3}=0,017 p_{2-3}=0,007**
Leukocytes, %	71 (57,25-75,75)	70,5 (60,5-77,5)	34 (29-41)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
Leukocytes, 10^9/l	3,94 (3,36-5,93)	4,01 (3,29-7,51)	4,25 (3,16-5,07)	
CD3+, %	43,5 (34,75-51)	46,5 (39,25-52,75)	50 (39-57)	
CD3+, 10^9/l	1,85 (1,3-2,57)	1,88 (1,33-3,16)	1,99 (1,39-2,57)	
CD19, %	12 (6,75-17,5)	14 (9,25-17)	15 (12,0-18,0)	**p_{1-2}=0,045**
CD19, 10^9/l	0,56 (0,24-1,16)	0,59 (0,42-0,8)	0,63 (0,36-0,97)	
CD4+, %	28,5 (23,75-38,25)	32,5 (25,25-39,25)	37 (29-43)	
CD4+, 10^9/l	1,07 (0,79-2)	1,25 (0,94-2,42)	1,47 (1,04-2,06)	
CD8+, %	11 (8,75-14,25)	13 (10,25-17)	15,5 (12-19)	
CD8+, 10^9/l	0,46 (0,26-0,69)	0,59 (0,45-0,85)	0,58 (0,43-0,61)	
CD4/CD8	2,8 (2,1-3,66)	2,32 (1,71-3,25)	2,39 (1,78-2,96)	
CD25+CD4+, %	3 (2-5)	4 (2-4,75)	3 (2-4)	
CD25+CD4+, 10^9/l	0,12 (0,08-0,26)	0,17 (0,12-0,34)	0,11 (0,09-0,18)	**p_{2-3}=0,012**

Note: *p1-2, p1-3, p2-3 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The results of phenotyping of leukocytes by flow cytofluorometry showed that mature T-lymphocytes with the CD3 phenotype accounted for more than 40% of cord blood lymphocytes in very premature infants of all examined groups. When comparing the indicators of the main subpopulations of T- and B-lymphocytes of the umbilical cord blood of the main groups, no significant differences were found.

One of the important results of activation is the expression of genes for growth factors and their receptors. Thus, an increase in the absolute number of regulatory cells with a receptor for IL-2, which is an activation marker (CD25 + CD4 +) (p_{2-3} = 0.012), was observed in newborns with ELBW 28-31 weeks of GA, which contributes to the implementation of accelerated differentiation of regulatory lymphocyte populations [13]. In children born at the time of very early preterm birth, the expression of the CD25 + / CD4 + receptor did not differ from that of full-term infants.

To characterize the balance of cytokine-producing lymphocytes of the first and second order, the ratio of the percentage of Th1- / Th2- lymphocytes (CD4 + IFN +, CD4 + IL-4 +) was determined, which was calculated for each representative of the age group in spontaneous and induced tests.

When analyzing the indices of intracellular cytokines of the umbilical cord blood in all premature infants, a decrease in the content of T-helpers spontaneously synthesizing IL-4 was noted (Table 16).

At the same time, the level of IFN-γ expression did not differ from that of the comparison group. The ratio of regulatory subpopulations producing Th1 and Th2 cytokines in all premature infants in the spontaneous test had a pro-inflammatory orientation and was 1.7 and 1.9 times higher than the indices of full-term infants ($p_{1-3.2-3}$ = 0.001). Upon cell stimulation, the polarization index significantly increased in premature infants with a shorter gestation period (p_{1-3} = 0.001).

Table 16.

The content of cytokine-producing cells in the umbilical cord blood of children with ELBW

Indicators	1 group (n=46)	2 group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me (25-75)	
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	2,89 (1,74-4,0)	2,36 (1,66-6,09)	2,36 (1,66-6,09)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	4,49 (2,69-6,34)	4,58 (1,64-7,67)	3,27 (1,17-6,83)	
$CD4^+IL\text{-}4^+$ self-existing, %	2,1 (0,91-3,02)	1,65 (0,83-3,17)	3,45 (2,71-4,97)	**$p_{1\text{-}3,\ 2\text{-}3}$=0,001**
$CD4^+IL\text{-}4^+$ suscitate, %	4,59 (2,73-5,42)	3,8 (2,97-5,13)	4,48 (3,89-6,53)	**$p_{1\text{-}3,\ 2\text{-}3}$=0,04**
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,35 (1,26-1,75)	1,56 (1,41-2,0)	0,79 (0,71-0,97)	**$p_{1\text{-}3,\ 2\text{-}3}$=0,0001**
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,2 (1,03-1,52)	1,19 (0,65-1,3)	1,05 (0,61-1,39)	**$p_{1\text{-}3}$=0,001**

Note: *p1-2, p1-3, p2-3 - significance of differences between groups of children: 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The hypoxic effect on the fetus in the antenatal period affects the change in immunological parameters, directly reflects the negative effect of placental insufficiency on the development of the immune response of children with ELBW. In children with GA of22-27 weeks, positive correlations were found between the development of subcompensated CPI in the mother and the content of cytokine-producing cells ($CD4^+$ $IL\text{-}4^+$ and $CD4^+$ $IFN\text{-}\gamma^+$, $r = 0.87$ at $p = 0.010$ in both cases), the presence of preeclampsia of moderate severity and the index of polarization of cytokine-producing cells upon stimulation ($r = 0.87$ at $p = 0.010$).

We found a correlation between the presence of children of the 1st group on ALV from birth and the level of regulatory cells ($CD25 + CD4^+$) ($r = 0.57$, $p = 0.001$) as well as the induced production of intracellular IL-4 ($r = 0.50$, $p = 0.01$) reflects the effect of oxygen deficiency on the formation of cytokine balance and the reserve of cytokine-producing cells.

By the end of the late neonatal period, a decrease in the number of leukocytes and relative lymphocytosis in the peripheral blood of all premature infants remained (Table 17).

Table 17.

The main subpopulations of peripheral blood lymphocytes in children with ELBW at the age of 1 month of life

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me (25-75)	
Leukocytes, 10^9/l	**6,9 (5,88-8,93)**	**7,38 (5,84-8,86)**	**10,85 (9-14,5)**	**p_{1-3}=0,0001 p_{2-3}=0,0001**
Lymphocytes, %	60 (47,5-65)	60 (51,5-74,25)	34 (29-41)	**$p_{1-2}\geq$0,05 p_{1-3}=0,0001 p_{2-3}=0,0001**
Lymphocytes, 10^9/l	4,28 (3,31-5,71)	4,35 (3,39-5,64)	4,25 (3,16-5,07)	
CD3+, %	54 (48-67)	55 (44-64)	50 (39-57)	
CD3+, 10^9/l	2,32 (1,56-2,85)	2,44 (1,89-3,2)	2,01 (1,56-2,66)	
CD19+, %	10,5 (8,0-16,75)	15 (9,0-20,0)	15 (12,0-18,0)	
CD19+, 10^9/l	0,49 (0,18-0,73)	0,51 (0,38-0,98)	0,63 (0,36-0,97)	
CD4+, %	40 (28,5-47)	40 (30,5-46)	37 (29-43)	
CD4+, 10^9/l	1,78 (1,18-1,95)	1,62 (1,29-2,06)	1,47 (1,04-2,06)	
CD8+, %	18 (14-24)	15,5 (12-19)	15,5 (12-19)	
CD8+, 10^9/l	0,68 (0,55-1,02)	0,58 (0,43-0,61)	0,58 (0,43-0,61)	
CD4/CD8	2,27 (1,1-2,93)	2,25 (1,89-2,89)	2,39 (1,78-2,96)	
CD25+CD4+, %	6 (4-7)	5,5 (4-6)	3 (2-4)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
CD25+CD4+, 10^9/l	0,2 (0,17-0,3)	0,26 (0,18-0,31)	0,11 (0,09-0,18)	**p_{1-3}=0,015 p_{2-3}=0,0001**

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The number of T- and B-lymphocytes and their subpopulations did not differ from those of full-term newborns.

During this period, all premature infants showed an increase in the relative and absolute number of regulatory cells with a receptor for IL-2, which is an activation marker ($CD25^+$ $CD4^+$) ($p^{1-3.2-3}$ <0.015), which contributes to the accelerated differentiation of regulatory lymphocyte populations.

By the age of 1 month of life, all premature infants had a reduced number of T-helpers producing IL-4, as a result of which the first order lymphocytes predominated in the pool, which is associated with antigenic stimulation with bacterial agents (Table 18).

Table 18.

The content of cytokine-producing cells in children with ELBW at the age of 1 month of life

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me (25-75)	
$CD4^+IFN\text{-}\gamma^+$ self-existing, %	2,02 (1,23-4,22)	2,52 (1,42-4,05)	2,36(1,66-6,09)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	4,04(12,58-6,16)	5,35(3,57-6,66)	3,27(1,17-6,83)	
$CD4^+IL\text{-}4^+$ self-existing, %	1,77 (0,91-3,1)	1,45 (1,03-2,49)	3,45(2,71-4,97)	**$P_{1\text{-}3,\ 2\text{-}3}$=0,0001**
$CD4^+IL\text{-}4^+$ suscitate, %	2,71 (1,7-3,44)	3,9 (2,8-4,73)	4,48(3,89-6,53)	**$P_{1\text{-}3}$=0,001 $P_{2\text{-}3}$=0,016**
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,35 (1,22-1,55)	1,77 (1,37-2,09)	0,79(0,71-0,97)	**$P_{1\text{-}3,\ 2\text{-}3}$=0,0001**
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,73(1,55-2,47)	1,31(1,17-1,66)	1,05(0,61-1,39)	**$P_{1\text{-}3}$=0,01 $P_{2\text{-}3}$=0,016**

Note: *p1-2 - the significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group*

Upon stimulation of cytokine-producing cells, the revealed changes persisted.

Upon reaching the post-conceptional age of 38-40 weeks in premature infants, the level of leukocytes remained reduced ($p_{1\text{-}3.2\text{-}3}$ = 0.0001), the relative number of lymphocytes - increased ($p_{1\text{-}3.2\text{-}3}$ = 0.0001), compared with full-term newborns, which indicates a high risk of an infectious process in children with ELBW (Table 19).

Table 19.

The main subpopulations of peripheral blood lymphocytes in children with ELBW at 38-40 weeks of PCA

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
Leukocytes, 109/ l	6,3 (5,32-6,8)	6,75 (5,8-8,55)	10,85 (9-14,5)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
Lymphocytes, %	68 (64-78,5)	68 (60-72)	34 (29-41)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
Lymphocytes, 109/l	4,35 (3,62-4,97)	4,62 (4,06-5,14)	4,25 (3,16-5,07)	
CD3+, %	51,5 (41,5-58,25)	50 (44-53)	50 (39-57)	
CD3+, 10^9/l	2,04 (1,66-2,69)	2,22 (2-2,57)	1,99 (1,39-2,57)	
CD19+, %	29 (17,25-33,75)	28 (21-31)	12 (8-15)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
CD19+, 10^9/l	1,22 (0,59-1,51)	1,22 (0,96-1,8)	0,36 (0,29-0,74)	**p_{1-3}=0,002 p_{2-3}=0,0001**
CD4+, %	31,5 (24-37,5)	33 (28-37)	37 (29-43)	
CD4+, 10^9/l	1,35 (1-1,73)	1,52 (1,26-1,83)	1,47 (1,04-2,06)	
CD8+, %	16,5 (13-23,5)	15 (12-19)	15,5 (12-19)	
CD8+, 10^9/l	0,65 (0,5-0,78)	0,65 (0,58-0,87)	0,58 (0,43-0,61)	
CD4/CD8	2,17 (1,42-2,56)	2,17 (1,63-3,08)	2,39 (1,78-2,96)	
CD25+CD4+, %	4 (3,5-5)	5 (4-5)	3 (2-4)	**p_{2-3}=0,02 p_{1-3}=0,0001**
CD25+CD4+, 10^9/l	0,17 (0,15-0,24)	0,22 (0,2-0,26)	0,11(0,09-0,18)	**p_{1-2}=0,036 p_{1-3}=0,0001**

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The relative number of subpopulations of T-lymphocytes in children of the main groups upon reaching PCA 38-40 weeks was comparable to the indicators of the comparison group.

The activation of the B-cell link of immunity was indicated by a significant increase in the number of B-lymphocytes in very premature infants with ELBW ($p_{1-3.2-3}$ = 0.001).

In premature infants with ELBW, an increase in both the relative and absolute number of regulatory cells with the $CD25^+/CD4^+$ receptor remained ($p_{2-3} = 0.012$).

The analysis of intracellular cytokines showed that upon reaching the age of a full-term child, a significantly reduced number of $CD4^+$ $IL\text{-}4^+$ cells in the spontaneous test remained in all children (Table 20).

Table 20.

The content of cytokine-producing cells in children with ELBW at 38-40 weeks of PCA

Indicators	1 group (n=42)	2 group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me (25-75)	
$CD4^+IFN\text{-}\gamma^+$ self-existing, %	3,08 (1,93-4,07)	2,85 (2,26-4,77)	2,36(1,66-6,09)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	6,3 (3,44-8,87)	3,88 (2,82-5,95)	3,27(1,17-6,83)	
$CD4^+IL\text{-}4^+$ self-existing, %	1,32 (1,25-3,2)	1,44 (1,08-2,3)	3,45(2,71-4,97)	**$P_{1-3,\ 2-3}$=0,0001**
$CD4^+IL\text{-}4^+$ suscitate, %	3,21 (2,06-5,56)	3,88 2,82-5,95)	4,48(3,89-6,53)	
$CD4^+IFN\text{-}\gamma^+$ / $CD3^+IL\text{-}4^+$ self-existing, c.u.	1,41 (1,27-1,77)	1,78 (1,57-1,97)	0,79(0,71-0,97)	**$p_{1-3,\ 2-3}$=0,0001** **p_{1-2}=0,018**
$CD4^{++}IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,96 (1,26-2,55)	1,05 (0,98-2,42)	1,05(0,61-1,39)	$p_{1-3,\ 2-3}$=0,017

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

When stimulating cytokine-producing cells, there were no significant differences with the indicators of umbilical cord blood in full-term infants. The ratio of the number of IFN- γ and IL-4 producing lymphocytes in all newborns with ELBW remained higher compared to those in full-term infants. The children of the 2nd group showed the maximum values of the cell polarization index in the spontaneous test.

Thus, the studies carried out made it possible to identify some regularities in the formation mechanism of innate and adaptive immunity. In all children with ELBW, regardless of gestational age, against the background of a decrease in the number of leukocytes, an increase in the relative number of lymphocytes was

found, which reflects the physiological process of "learning" of many clones of T and B cells carrying TCR receptors for recognizing foreign antigens. The absence of significant differences in the number of CD3-, CD19-, CD4- and CD8 - populations, indicates the achievement of the required number of mature cells in the development of the cellular link of immunity in the main populations of lymphocytes by 22 weeks of gestational age.

The development of the immune response towards a Th1-dependent cellular or Th2-humoral response directly depends on the induction of the cytokine signal received by the cells. When studying the production of intracellular cytokines in premature infants, a decrease in the number of cytokine-producing $CD4^+$ IFN-γ^+ cells was found regardless of the presence or absence of lymphocyte stimulation. That resulted in an increase in the polarization index ($CD4^+$ IFN-γ^+/$CD4^+$ IL-4^+) cells and the inflammatory direction of the immune response. An increase in the polarization index (IFN-γ/IL-4) more than 1.0 was recorded in children with ELBW in 95.7% and 97% of cases, respectively. In full-term infants, the shift in the balance of cytokine-producing cells towards the Th2-dependent immune response was dominant in 72.3% of cases, respectively ($p < 0.017$). The revealed changes persisted throughout the entire period of nursing premature babies. Nevertheless, at the age of 1 month in children with ELBW, the number of regulatory cells expressing the IL-2R ($CD25^+$) receptor increases, and upon reaching PCA 38-40 weeks, the proportion of B-lymphocytes increases in comparison with the indicators of term infants, which indicates "maturity" of cellular responses of adaptive immunity.

It should be noted a statistically significant decrease in the number of cells producing IL-4 in children born at the time of very early preterm labor, which indicates inhibition of early cell activation processes and indicates a shift in the balance of immunocompetent cells in favor of systemic suppression.

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3.2. Study of innate immunity indices in children with extremely low body weight in the dynamics of the postnatal period

The prospects for the full rehabilitation of deeply premature children are largely determined by immunological mechanisms [1]. It has been proven that the child's immune system plays a leading role in the pathogenesis, clinical course and outcome of hypoxic and infectious diseases. Immaturity of the immune system due to the violation of the evolutionarily determined course of postnatal adaptation under conditions of increased antigenic load in the perinatal period prevents the development of an overreaction. The mechanisms of innate immunity prevent

the development of the infectious process at the earliest stages as a result of the rapid elimination of pathogens, when the mechanisms of adaptive immunity are not yet function [2]. The factors of innate immunity include cells of the monocytic-macrophage link, neutrophils, the complement system, natural killer cells and cytokines produced by these cells, the factors of adaptive immunity - T- and B-lymphocytes and their subpopulations, immunoglobulins of various classes.

Monocytes and macrophages, derived from a common myeloid precursor, play an important role in the immune system [3]. In response to differentiation factors, some monocytes migrate and fill the tissues of the body, thereby avoiding apoptosis. Monocytes and their precursors can activate or inhibit the immune response, depending on local and systemic signals [4].

The key role in ensuring the reactions of innate immunity belongs to the cytokine system, which carries out intercellular interaction between innate and adaptive links of immunobiological control [5, 6]. Disruption of the balance of pro- and anti-inflammatory cytokines necessary for the formation of adequate adaptive immunity, systemic mechanisms of the body's natural resistance can lead to significant local activation of the inflammatory process and even its generalization, followed by rapid depletion [2, 6, 7], which subsequently leads to the development of multiple organ failure. In some cases, the determination of cytokines allows them to be used as criteria for the diagnosis and prediction of morbidity and mortality in newborns, differentiating infectious and non-infectious pathologies, improving the differential diagnosis of various inflammatory diseases [8, 9, 10, 11, 12]. Thus, most researchers conclude that, along with the level of procalcitonin and C-reactive protein (CRP), the indicators of IL-6, -8, tumor necrosis factor-α (TNF-α) are the earliest and most specific markers of sepsis in newborns [13, 14, 15]. High levels of IL-6 in umbilical cord blood are associated with an increased risk of morbidity and mortality in the newborn [9, 16]. According to T.G. Kredient there is a relationship between increased levels of IL-6 and IL-8 with RDS-associated inflammation and early peri / intraventricular hemorrhages [17]. The data of foreign authors indicate a significant dependence of high levels of proinflammatory cytokines in the blood serum of premature infants who developed PVL [18, 19]. Excessive production of IL-4, IL-8, TNF-α in hypoxic conditions of the brain in newborns can lead to secondary periventricular necrosis and are associated with an unfavorable course of the disease [20, 21]. In recent years, data have appeared proving the polymorphism of genes encoding the excessive production of proinflammatory cytokines IL-6, IL-8, TNF-α and, thereby, a genetic predisposition to PVL and cerebral palsy [10]. From the point of view of genetics, the development of BPD is determined by a complex interaction of various genes and environmental factors [22]. Regardless of the multifactorial etiology, the pathogenesis of BPD is based on inflammation, which subsequently progresses. Cytokines, modulating the immune defense, are involved in the normal development of lung tissue and, during the development of BPD, mediate acute lung injury, aggravating ventila-

tion-associated lung damage [23].

In a study by N. Ambalavanan et al. (2009) it was found that children with ELBW at birth had high serum concentrations of some cytokines (interleukin (IL) 1β, IL-6, IL-8, IL-10, interferon-γ (IFN-γ)) and low concentrations other cytokines (IL-17; chemokine expressed and secreted by T cells upon activation (RANTES). Tumor necrosis factor-β) have been associated with the development of BPD and death [24].

It was found in the work of A. K. Maksutova that the level of IL-4 production in children with congenital generalized infections does not depend on the gestational age of newborns, while the level of pro-inflammatory cytokines (IFN-γ, TNF-α) is higher in full-term children. [25].

As an anti-infectious defense, the importance of the interferon system, which is of great importance in the formation of immunity, is increasing [26, 27]. In the study of V. A. Pertseva a tendency towards suppression of interferonogenesis was noted in children with ELBW, during the formation of infectious and inflammatory diseases [28].

The innate immune system plays an important role in the pathogenesis of infectious and inflammatory diseases. The formation of the child's immune response and resistance to increased microbial colonization is determined by the functioning of cellular factors of nonspecific resistance (micro- and macrophages). Cells of the myeloid series, including monocytes, are involved in the implementation of the effector mechanisms of the innate immunity of premature infants, including monocytes, on the ability of which to phagocytosis depends on the blocking of vital activity, disintegration and removal of the pathogen from the body.

The phagocytosis process can be divided into several stages: object recognition, activation, chemotaxis, adhesion, phagocytosis, digestion, antigen presentation.

The activation of positive CD64 neutrophils is considered an early sign of an immune response to a bacterial infection, which occurs approximately one hour after an infectious invasion. It was found that the expression of CD64 is increased in blood samples from newborns with sepsis [29]. Determination of CD64 demonstrates a greater degree of sensitivity than the method for determining C-reactive protein or IL-6, both in early and late forms of sepsis [30].

The CD11b marker mediates inflammation by regulating leukocyte adhesion and migration [31]. In the case of the development of an infectious process, the expression of CD11b increases on neutrophils and monocytes. It has been found that CD11b is a very effective marker in the diagnosis of early onset neonatal infection. Compared with uninfected newborns, the expression of the receptor in sepsis is increased [32, 33].

HLA-DR protein is a class II receptor of the MHC histocompatibility complex, which forms a ligand for the T-cell receptor of T-helper cells. According to Kanakoudi-Tsakalidou data, the HLA-DR expression on monocytes can be criti-

cal also in the presence of respiratory distress syndrome [34]. At the same time, a decrease in the HLA-DR expression on circulating monocytes was observed in newborns with sepsis [35].

An important factor contributing to the adequate preparation of monocytes for the uptake of various foreign particles is the CD11b expression receptor by cells involved in the formation of contacts of leukocytes with the vascular endothelium, regulation of the inflammatory response, provision of intracellular signal transmission, and activation of leukocytes [36, 37].

Examination of indices of innate immunity in all premature infants revealed a significant decrease in the relative number of $CD14^+CD11b^+$ monocytes, which indicates the predominance of immature cells in the population and reflects a reduced readiness of effector cells to participate in the processes of antigen presentation and intercellular interaction [74] (Table 21).

Table 21.

Activation markers of umbilical cord blood monocytes in premature infants with ELBW

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
CD11b+CD14+, %	30,0 (15,0-62,0)	37,0 (27,75-49,75)	70 (67,0-77,0)	**$p_{1-3, 2-3}$=,0001**
CD11b+CD14+, abs.	0,15 (0,08-0,18)	0,19 (0,14-0,20)	0,39 (0,37-0,95)	**$p_{1-3, 2-3}$=0,010**
CD64+CD14+, %	17 (8,0-34,0)	40 (24,5-43,5)	58,0 (33,5-71,0)	**p_{1-3}=0,017**
CD64+CD14+, 10^9/l	0,05 (0,04-0,16)	0,15 (0,11-0,22)	0,46 (0,35-0,72)	**p_{2-3}=0,021** **p_{1-3}=0,009**
CD14+HLA-DR+, %	21 (10,5-29)	33 (22-58)	53 (38-63,5)	**p_{1-2}=0,014** **p_{1-3}=0,0001** **p_{2-3}=0,057**
CD14/HLA-DR, 10^9/l	0,09 (0,05-0,14)	0,13 (0,075-0,18)	0,5 (0,34-0,84)	**p_{1-3}=0,001** **p_{2-3}=0,002**
CD71+CD14+, %	17 (11,0-19,5)	16 (12,0-44,0)	18,0 (16,5-21,5)	
CD71+CD14+, 10^9/l	0,18 (0,12-0,24)	0,18 (0,14-0,29)	0,21 (0,18-0,25)	

Note: *p1-2, p1-3, p2-3 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

In premature infants, there was a significant decrease in the absolute number of $CD64^+$ $CD14^+$ cells compared to full-term infants ($p_{1-3} = 0.009$, $p_{2-3} = 0.021$). A decrease in the percentage of activated monocytes was found in children of the 1st group.

HLA-DR belongs to class II molecules of the major tissue histocompatibility complex, which are responsible for the presentation of antigen to T cells. When comparing the indices of innate immunity of newborns of the main groups, a significant decrease in the percentage of CD14 + HLA-DR + in children of gestational age of 22-27 weeks was revealed ($p_{1-2} = 0.014$, $p_{1-3} = 0.0001$, $p_{2-3} = 0.057$), which, according to a number of authors, it correlates with an increase in the risk of infectious pathology. Correlation analysis revealed a strong positive relationship between the development of sepsis and the level of CD14 + HLA-DR + in umbilical cord blood in children of the 1st group ($r = 0.73$, $p = 0.004$), as well as the formation of a severe form of BPD in children of the 2nd groups ($r = 0.52$, $p = 0.018$). It is known that sepsis actively affects the decrease in HLA-DR on monocytes and glucocorticoids [38]. However, both main groups of women received antenatal prophylaxis of RDS with dexazone in 100% of cases.

The transferrin receptor (CD71+) is an early activation marker, and an increase in its expression level is observed on proliferating cells. The relative number of monocytes carrying the transferrin receptor CD71/CD14 in the main groups of children corresponded to the values of full-term infants.

In addition to monocytes, cells of innate immunity include natural killer cells (NK) - large granular lymphocytes that have the ability to destroy the virus infected cells. Statistically significant differences in percentage (4 (2-9) and 6 (3-12)% in the 1st and 2nd groups, versus 5 (3-6.75)% in the 3rd group, $P_{1-2, 2-3} \geq 0.05$) and absolute (0.13 (0.08-0.61) and 0.24 (0.082-0.58) 10^9/l versus 0.18 (0.12-0.29)) 10^9/l indices of NK cells in the umbilical cord blood of premature and full-term infants, not detected

The study of pro- and anti-inflammatory cytokines in the serum of umbilical cord blood showed that all preterm infants are diagnosed with a significant increase in the level of pro-inflammatory cytokines: IFN-γ and IL-8, which are predictors of the infectious process ($p_{1-3, 2-3} = 0.0001$ in all cases) (Table 22).

Table 22.

Levels of cytokines and acute phase proteins of the umbilical cord blood of the examined children

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
IFN- γ, pg/ml	12,14 (10,81-13,68)	10,33 (2,83-11,94)	1,57 (0,87-2,8)	$p_{1-2, 1-3, 2-3}$=0,001
IL-6, pg/ml	101,5 (11,16-147,3)	8,74 (3,95-16,31)	6,79 (3,56-14,77)	$p_{1-3, 1-2}$=0,001
IL-8, pg/ml	88,54 (71,2-158,1)	25,9 (15,4-55,6)	12,02 (6,75-15,06)	$p_{1-3, 2-3}$=0,001 p_{1-2}=0,01
IL-4, pg/ml	0,61(0,48-0,87)	0,77 (0,55-0,98)	3,33 (2,87-3,47)	$p_{1-3, 2-3}$=0,0001

Note: *p1-2, p1-3, p2-3 - the significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

In contrast, IL-4 level was significantly reduced in both main groups. The increased concentration of IL-6 was recorded only in newborns of gestational age of 22-27 weeks, exceeding the indicators of children of the 2nd and 3rd groups by almost 11 times.

At the age of 1 month of life, the number of activated monocytes in premature infants significantly increased, reaching the values of the comparison group (Table 23).

All premature infants had a significant increase in the percentage of CD14 + HLA-DR + cells (p_{1-3} = 0.01, p_{2-3} = 0.002) relative to the parameters of the cord blood and the values of the comparison group. At the same time, the level of $CD16^+CD56^+$ -cells in children of the main groups, as in absolute (0.44 (0.3-0.75) and 0.36 (0.27-0.61) 10^9/L versus 0.18 (0.12-0.29) 10^9/L p_{1-3} = 0.002, p_{2-3} = 0.018), and in relative values (11 (8-16.5) and 9 (7-14)% versus 5 (3 -6.75)%, $p_{1-3, 2-3}$ = 0.001) significantly exceeded the children's indicators of the 3rd group, which may be associated with a reaction to antigenic stimulation with bacterial agents.

Table 23.

Activation markers of peripheral blood monocytes in children with ELBW at 1 month of life

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me(25-75)	
CD11b+CD14+ %	59,5(49,5-78,5)	67,0(62,0-80,5)	70(67,0-77,0)	
CD11b+CD14+, abs.	0,47(0,33-0,69)	0,49(0,36-0,61)	0,39(0,37-0,95)	
CD64+CD14+, %	20 (4,75-41)	21 (10-55,5)	58,0 (33,5-71,0)	
CD64+CD14+ 10^9/l	0,14 (0,04-0,3)	0,22 (0,06-0,37)	0,46 (0,35-0,72)	
HLA-DR+ CD14+, %	67 (54-77,5)	67 (59-70,5)	53 (38-63,5)	**p_{1-3}=0,01 p_{2-3}=0,002**
HLA-DR+ CD14+, 10^9/l	0,45 (0,28-0,8)	0,46 (0,35-0,58)	0,5 (0,34-0,84)	
CD71+CD14+, %	14 (6,5-15)	13 (6-23,5)	18,0 (16,5-21,5)	
CD71+CD14+, 10^9/l	0,08 (0,05-0,11)	0,09 (0,04-0,16)	0,21 (0,18-0,25)	

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

By the age of 1 month of life, IL-4 production in all premature infants increased relative to the initial level. However, it remained significantly lower than in the comparison group (Table 24).

Table 24.

Peripheral blood cytokine levels in premature infants with ELBW at the age of 1 month of life

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
IFN- γ, pg/ml	3,77 (0,55-7,03)	2,76 (0,55-5,55)	1,57(0,87-2,8)	
IL-6, pg/ml	5,63 (4,6-10,97)	5,82 (4,08-14,06)	6,79 (3,56-14,77)	
IL-8, pg/ml	27,9 (23,29-36,95)	19,35 (12,77-28,3)	12,02 (6,75-15,06)	**$p_{1-3,\ 2-3}$=0,001**
IL-4, pg/ml	1,6 (1,37-1,79)	1,91 (1,55-2,06)	3,33 (2,87-3,47)	**$p_{1-3,\ 2-3}$=0,0001**

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The amount of IFN-γ and IL-6 in children of the main groups did not differ from the indicators of full-term newborns. The concentration of IL-8 decreased slightly, but remained stably high.

The results of the study of markers of monocyte activation are presented in table 25.

An increased number of monocytes expressing the $CD14^+$ $HLA\text{-}DR^+$ receptor and the $CD11b^+$ $CD14^+$ adhesion molecule were observed in the peripheral blood of premature infants upon reaching PCA 38-40 weeks. In children of the 2nd group there was an increase in the relative number of $CD64^+CD14^+$ -monocytes, compared with the same indicators of children of the 1st and 3rd groups. The increased content of CD14 / HLA-DR monocytes positively correlated with the presence of pneumonia in children with lower ELBW at the age of 1 month of life (r = 0.48, p = 0.03).

Table 25.

Markers of peripheral blood monocyte activation in children with ELBW at PCA 38-40 weeks

Indicators	1 group (n=42)	2 group (n=43)	3rd group (n=25)	p
	Me(25-75)	Me(25-75)	Me(25-75)	
CD11b+CD14+, %	77 (73,0-78,75)	82 (78-85)	69 (60,5-80,5)	**p_{1-3}=0,017 p_{2-3}=0,001 p_{1-2}=0,047**
CD11b+CD14+, abs.	0,24 (0,23-0,51)	0,54 (0,47-0,58)	0,36 (0,14-0,71)	
CD64+CD14+ %	25,5 (17,5-39,5)	73 (65-87)	58,0 (33,5-71,0)	**$p_{1-2, 2-3}$=0,010**
CD64+CD14+, 10^9/l	0,14 (0,13-0,35)	0,5 (0,43-0,6)	0,46 (0,35-0,72)	
CD14+HLA-DR+, %	74 (64-82)	75 (63-80)	53 (38-63,5)	**p_{1-3}=0,0001 p_{2-3}=0,0001**
CD14+HLA-DR+, 10^9/l	0,35 (0,28-0,55)	0,52 (0,42-0,66)	0,5 (0,34-0,84)	**p_{1-2}=0,09**
CD71+CD14+, %	14 (10-22,5)	16 (10-20)	18,0 (16,5-21,5)	

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

The increased relative number of NK cells in 1 month of life remained at a significantly high level in PCA 38-40 weeks (13 (7.25-20.5) and 13 (9-17)% versus 5 (3-6.75) %, $p_{1-3, 2-3} = 0.001$; 0.52 (0.3-0.76) and 0.64 (0.31-0.78) 10^9/l versus 0.18 (0.12-0, 29) 10^9l, $p_{1-3, 2-3} = 0.001$).

Upon reaching the post-conceptional age (37-40 weeks), all premature infants retained a reduced level of IL-4 (Table 26).

Table 26.

Levels of cytokines and acute phase proteins of peripheral blood of the examined children in PCA 38-40 weeks

Indicators	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	p
	Me (25-75)	Me (25-75)	Me (25-75)	
IFN- γ, pg/ml	0,83 (0-3,6)	2,74 (0-5,69)	1,57(0,87-2,8)	
IL-6, pg/ml	3,78 (2,6-4,58)	5,1 (2,97-12,4)	6,79 (3,56-14,77)	**$p_{1-3,}$=0,001**
IL-8, pg/ml	14,71 (10,56-26,8)	12,82 (11,9-29,02)	12,02 (6,75-15,06)	
IL-4, pg/ml	2,05 (1,75-2,70)	2,22 (1,96-2,46)	3,33 (2,87-3,47)	**$p_{1-3, 2-3}$=0,001**

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation, 3 - comparison group.*

At the same time, in children of the main groups, a decrease in the concentration of IL-8 was observed, to the level of full-term newborns, and in children of the 1st group, the content of IL-6 was 2 times lower than in the comparison group ($p_{1-3} = 0.001$).

As a result of our studies, we have demonstrated that the spectrum of monocyte-macrophage protection factors in children with ELBW at birth was significantly limited due to a decrease in adhesion and migration of cells to the inflammation focus ($CD14^+CD11b^+$, $CD14^+$ $CD64^+$), as well as the presentation of infectious pathogens (CD14HLA -DR), which indicates a violation of coordination between innate and adaptive immunity and may be the cause of the development of bacterial complications and a prolonged course of the inflammatory process.

By the time of transfer of children with ELBW to the stage of early rehabilitation, the inclusion of effector mechanisms of the cellular link of immunity was established - an increase in the percentage of NK cells, the level of which remained after reaching PCA for 38-40 weeks. The ability of monocytes to recognize infectious pathogens and a full-fledged antigen-presenting function was restored. The number of cells expressing signaling molecules (CD11b and CD64) in children of the main groups did not differ, and the relative number of CD14+HLA-DR+ cells exceeded the indices of term infants both at the end of the neonatal period and in PCA 38-40 weeks.

In the course of the immune response, the cytokine system - products of activated immunocompetent cells mediates the regulation of intercellular interactions.

Another common feature of the innate immunity of children with ELBW is the predominance of pro-inflammatory cytokine factors in the cord blood serum that determine the nature of the immune response (Th1-dependent response): an increased concentration of IL-8 at birth and a decreased content of IL-4, which persists after reaching PCA 38- 40 weeks.

Thus, the formation of the immune system response in the postnatal period of premature infants with ELBW does not depend on GA. The revealed highest content of serum IFN-γ, IL-6 and IL-8 in newborns at GA of 22-27 weeks at birth indicates the activation of the immune system in the antenatal period, due to the presence of risk factors for the development of infectious pathology of mothers (chorioamnionitis, prolonged anhydrous period, premature rupture of the membranes).

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3.3. Evaluation of local immunity in children with extremely low body weight

Intestinal microbiota formation is a multi-step process that plays an important role in the maturation of the immune system in newborn babies. To activate local immunity, as well as the immune system of the whole organism against the background of the formation of an adequate immune response, it is necessary to influence the antigens of the normoflora [1, 2].

There is evidence in the publication that in the second half of pregnancy, the intestinal microflora is formed in the fetus through the phenomenon of bacterial translocation [3].

Colonization of the intestine by microbiota determines the balance of T-helper cells (Th1 and Th2), while the prevalence of one pathway or another contributes to the development of atopic and infectious diseases. Under normal conditions, there is a regulation and selectivity of defense mechanisms that control intestinal colonization and determine either immunological tolerance or the development of an immune response to pathogens [4].

The pathological course of the ante- and intranatal periods, infection, morphofunctional immaturity, hypoxia and asphyxia, invasive medical procedures, delayed breastfeeding in children with ELBW contribute to impaired colonization of the gastrointestinal tract [4].

Colonization of the intestine by the microflora in term and premature infants has significant differences [5]. In children with ELBW, there is no transformation of the intestinal microbiota with the dominance of indigenous flora, especially in the provision of resuscitation care. Therefore, environmental factors become lead-

ing in the formation of microbial colonization. The leading places among various species are occupied by Coliforms, Enterococcus, Bacteroides, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Staphylococcus [5, 6].

In the reference, there are isolated works devoted to the study of systemic and local immunity in newborns with ELBW during early rehabilitation. After birth, under the influence of pathogens and immunological factors of breast milk, local immunity of the mucous membranes of the digestive tube is formed [7, 8, 9]. A number of studies have shown the relationship between increased IgA, IgM, IgG in blood serum and IgA, IgG in coprofiltrates in children from mothers with a long anhydrous period, STDs identified during pregnancy [10, 11]. By the end of the neonatal period, there was an increase in the frequency of detection of sIgA, IgG in coprofiltrates, as well as an increase in the concentration of serum immunoglobulins A and M. There is as well a decrease in immunoglobulin G in the blood serum in comparison with indicators at birth, which is possibly due to the destruction of maternal immunoglobulin G and the synthesis of own immune proteins [11]. There are practically no studies of the content of cytokines in coprofiltrates, which characterize the state of local immunity of children.

The immaturity of the child's immune system is replenished by passive immunity transmitted from the mother to the newborn. Passive immunity is provided by maternal immunoglobulins and protective factors in breast milk.

During the period of early microbial colonization of the intestine, the formation of the adaptive link of immunity begins in a child, a significant role in this process is assigned to bifidobacteria and lactobacilli, which trigger the production of cytokines by activated phagocytic cells [12].

Changes in the qualitative and/or quantitative composition of the intestinal microflora affect the Th1/Th2 balance of helper cells, determining immunological tolerance relative to normal microbiota or the immune response to pathogens [13].

By the time of transfer to the second stage of nursing, the intestines of children were colonized on average, in 70.8% of cases by pathogenetic microorganisms presented in Table 27.

Table 27.

Frequency of detection of opportunistic pathogens in feces in children with ELBW at the age of 1 month

Microflora	CFU/g	1 group (n=35)		2 group (n=40)		P
		Abs.	%	Abs.	%	
Microflora not identified		10	28,5	12	30	P_{1-2}=0,003
Microflora identified		**25**	**71,5**	**28**	**70**	P_{1-2}=0,005
Enterobacter cloacae	< 10^5	2	5,7	0	0	
	>10^5	1	2,9	1	2,5	
Enterobacter aerogenes	< 10^5	0	0	0	0	
	>10^5	0	0	2	5	
Klebsiella pneumoniae	< 10^5	1	2,9	1	2,5	
	>10^5	2	5,7	3	7,5	
Klebsiella oxytoca	< 10^5	0	0	0	0	
	>10^5	0	0	2	5	
Escherichia coli	< 10^5	0	0	0	0	
	>10^5	2	5,7	3	7,5	
Stenotr. Maltophilia	< 10^5	0	0	0	0	
	>10^5	1	2,9	1	2,5	
Pseudomonas spp.	< 10^5	2	5,7	0	0	
	>10^5	1	2,9	1	2,5	
S. epidermidis	< 10^5	6	17,1	4	10	
	>10^5	1	2,9	0	0	
S. haemolyticus	< 10^5	0	0	0	0	
	>10^5	0	0	3	7,5	
Enterococcus faecium	< 10^5	2	5,7	4	10	
	>10^5	2	5,7	2	5	
Genus of yeasts - *Candida*	< 10^5	1	2,9	0	0	
	>10^5	0	0	0	0	
Mixed flora	< 10^5	0	0	0	0	
	>10^5	1	2,9	1	2,5	

Note: *p1-2 - the significance of differences between groups of children ($\chi 2$ test with Yates' correction): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

The frequency of detection of enterobacteria (*Enterobacter cloacae, Klebsiella pneumoniae, Escherichia coli*) and non-fermenting gram-negative bacteria (*Stenotrophomonas maltophilia, Pseudomonas spp.*) was 34.2% in group 1. The total share of gram-positive bacteria (*Staphylococcus epidermidis, Enterococcus faecium*) is 28.5%. The frequency of detection of gram-negative and gram-positive microorganisms was practically the same in group 2. Enterobacteriaceae (Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli) and non-fermenting gram-negative bacteria (*Stenotrophomonas maltophilia, Pseudomonas spp.*) were observed in 35% of cases. The detection rate of coagulase-negative staphylococci (*Staphylococcus haemolyticus, Staphylococcus epidermidis*) and enterococci (*Enterococcus faecium*) was 32.5%. Mixed flora was detected in both groups of children with almost the same frequency of 2.9% (*Candida kruzei* 10^5 *and Staphylococcus epidermidis* 10^5 *CFU/g*) and 2.5% (*Klebsiella oxytoca* 10^6 and *Citrobacter frendii* 10^6 CFU/g) cases, respectively.

It should be noted that microorganisms of the Enterobacteriaceae family and non-fermenting bacteria (Stenotr. Maltophilia and Pseudomonas spp.), potentially dangerous in terms of the formation of antibiotic resistance, were detected in almost every fourth child of both groups (25.7% and 27.5%, respectively)

By PKA 38-40 weeks, intestinal microflora was found in all children from group 1 (Table 28).

Table 28.

Frequency of detection of opportunistic microflora in feces in children with ELBW at the post-conceptional age of 38-40 weeks

Microflora	CFU/g	1 group (n=29)		2 group (n=29)		P
		Abs.	%	Abs.	%	
Microflora not identified		0	0	7	24,1	**P_{1-2}=0,003**
Microflora identified		29	100	22	75,8	**P_{1-2}=0,005**
Enterobacter cloacae	$< 10^5$	0	0	0	0	
	$>10^5$	1	3,4	0	0	
Klebsiella pneumoniae	$< 10^5$	0	0	1	3,4	
	$>10^5$	6	20,7	3	10,3	
Klebsiella oxytoca	$< 10^5$	0	0	0	0	
	$>10^5$	2	6,9	1	3,4	
Escherichia coli	$< 10^5$	0	0	0	0	
	$>10^5$	3	10,3	2	6,9	
Pseudomonas spp.	$< 10^5$	0	0	1	3,4	
	$>10^5$	0	0	0	0	

S. epidermidis	$< 10^5$	4	13,8	1	3,4	
	$>10^5$	0	0	0	0	
Enterococcus faecium	$< 10^5$	2	10,3	4	13,8	
	$>10^5$	3	10,3	1	3,4	
Mixed flora	$< 10^5$	2	6,9	2	6,9	
	$>10^5$	4	10,3	4	13,8	

Note: *p1-2 - significance of differences between groups of children ($\chi 2$ test with Yates' correction): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

The total proportion of gram-positive microorganisms decreased to 17.2% of cases, and the detection rate of enterobacteriaceae and gram-negative non-fermenting bacteria increased to 62%.

In the 2nd group of children, the intestines were colonized in 75.8% of cases. At the same time, the proportion of gram-negative microorganisms remained at the same level (34.4%), compared with the age of one month. The detection rate of coagulase-negative staphylococci and enterococci decreased 1.6 times and amounted to 20.7% of cases in both groups. The number of cases of microbial associations detected at the age of a full-term baby in groups 1 and 2 increased 7.1 and 8.2 times (20.6% of cases).

The number of children with microorganisms of the family Enterobacteriaceae and non-fermenting bacteria in the 1st group increased by 12.2% (up to 37.9%), and in the 2nd group did not change and amounted to 27.5%.

Thus, a decrease in the amount of coccal microflora and an increase in the proportion of opportunistic enterobacteria were observed, the release of which from feces by the post-conceptional age was 100% and 75.9% in both groups in all very premature infants with ELBW, against the background of systemic antibiotic therapy, upon reaching 1 month of life. Intestinal colonization by enterobacteriaceae and non-fermenting gram-negative bacteria in children of group 1 was 1.6 times higher than in children of group 2 (62% versus 38%). At the same time, in 24.1% of children of the 2nd group, the intestines were not colonized. The share of mixed intestinal flora in children of the 1st and 2nd groups increased to 20.7%.

When analyzing the state of local immunity of children with ELBW, depending on the gestational age of the child, it was found that the content of IFN-γ in coprofiltrates in deeply premature infants during the entire stage of early rehabilitation significantly exceeded the indicators of the comparison group (Table 29).

Table 29.

The level of cytokines in the dynamics of the postnatal period in coprofiltrates in children with ELBW, IU (P25-P75)

Indicators, pg/ml	Age	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	P
IFN-γ	5-7 days	7,47 (6,63-7,58)	6,42(6,10-7,05)	5,68(0-5,89)	$p_{1-3, 2-3}$=0,0001
	1 month	6,32 (5,48-7,06)	5,37 (4,95-5,84)	5,68(0-5,89)	$p_{1-3, 2-3}$=0,0001 p_{1-2}=0,09
	PKA 38-40	6,22 (5,23-7,27)	5,79 (5,16-8,0)	5,68(0-5,89)	$p_{1-3, 2-3}$=0,0001
IL-6	5-7 days	3,0 (2,66-3,12)	3,11 (2,88-3,29)	6,12 (5.54-6.47)	$p_{1-3, 2-3}$=0,0001
IL-6	1 month	2,94 (2,89-3,23)	3,1293,02-3,230	6,12 (5.54-6.47)	$p_{1-3, 2-3}$=0,0001 p_{1-2}=0,012
	PKA 38-40	3,06 (2,89-3,13)	3,12(2,89-3,29)	6,12 (5.54-6.47)	p_{1-3}=0,06 p_{2-3}=0,03
IL-8	5-7 days	2,23 (2,18-3,85)	2,56 (2,17-2,86)	5.81 (2.82-5.9)	$p_{1-3, 2-3}$=0,0001
	1 month	2,31 (2,3-2,48)	2,22 (2,18-2,55)	5.81 (2.82-5.9)	$p_{1-3, 2-3}$=0,0001
	PKA 38-40	2,44 (2,2-3,85)	2,56 (2,24-2,82)	5.81 (2.82-5.9)	P_{2--3}=0,001
IL-4	5-7 days	34,33 (22,67)	31,49 (25,91-46,95)	4,33 (3,24-4,48)	$p_{1-3, 2-3}$=0,0001
	1 month	23,95 (16,69-34,08)	12,47 (2,31-60,18)	4,33 (3,24-4,48)	$p_{1-3, 2-3}$=0,010
	PKA 38-40	32,33 (20,88-61,48)	35,39 (27,27-50,81)	4,33 (3,24-4,48)	$p_{1-3, 2-3}$=0,001

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

There was a decreased content of IL-6 - statistically significant in the neonatal period and at the level of the tendency to PCA 38-40 weeks. The lowest concentration of this chemokine was observed in children of the 1st group at 1 month of age. In all children with ELBW in the early period of adaptation, there was a decrease in the concentration of IL-8, in children of the 2nd group, the revealed changes persisted until PCA 38-40 weeks. In the dynamics of the observation period from the first week of life, all premature infants had a significantly high content of IL-4. It may indicate the importance of opportunistic microorganisms, their species

diversity in the activation of the humoral link of immunity, the implementation of local protective mechanisms (activation of chemotaxis, limitation of the focus of inflammation, increasing the cytotoxic ability of macrophages).

The degree of protection against bacterial and viral infections of the gastrointestinal tract depends on the sIgA content, the main function of which is to neutralize toxins and viruses. Increased production indicates the development of an infectious process. As a result of the studies, it was found that the content of the sIgA level in coprofiltrates in children with ELBW at different periods of the study exceeded the standard values (0.5-2.0 g / l), which may be due to the activation of humoral immunity in the antenatal period (Table 30).

Table 30.

The content of sIgA in coprofilters in children with ELBW in the dynamics of the postnatal period, g/l

Time schedule	1st group (n=42)	2nd group (n=43)	3rd group (n=25)	Significance level
5-7 days	9,07 (6,94-12,82)	12,67 (6,53-13,70)	1,08 (1,03-3,36)	$P_{1-3, 2-3}$=0,0001 P_{1-2}=0,09
1 month	10,44 (8,89-10,97)	9,7 (9,58-10,71)	1,08 (1,03-3,36)	$P_{1-3, 2-3}$=0,0001
PCA 38-40 weeks	10,03 (5,97-11,12)	8,77 (6,5-10,02)	1,08 (1,03-3,36)	$P_{1-3, 2-3}$=0,0001

Note: *p1-2 - significance of differences between groups of children (Mann-Whitney test): 1 - children, 22 - 27 weeks of gestation, 2 - children 28 - 31 weeks of gestation.*

It should be noted that on the 5-7th day of life in children of gestational age of 22-27 weeks, there was a tendency to an increase in sIgA, compared with the indicators of newborns of the 2nd group. In further periods of life there were no significant differences between the main groups of children.

When conducting correlation analysis, it was found that the presence of opportunistic microflora in the intestine of a child in the early neonatal period positively correlates with the sIgA level in coprofiltrates at the age of 1 month of life ($r = 0.32$, $p = 0.04$), as well as with the content of IL-4 in 38-40 weeks of PCA.

It is known that breast milk is characterized by a high content of sIgA, the main function of which is to protect the GIT mucus membrane from pathogens of intestinal infections. We found direct correlations between breast milk production when feeding children with conditionally pathogenic intestinal microflora in the early neonatal period and at the age of 1 month of life with sIgA level in coprofiltrates ($r = 0.76$ and $r = 0.67$ at, $p = 0.001$). It possibly indicates the infection of the child in the antenatal period with the help of the phenomenon of bacterial translocation, when the maternal microorganisms entering the fetus in the second half of pregnancy cause the formation of an immune response.

By the time of transfer to the stage of early rehabilitation in premature infants with ELBW against the background of systemic antibacterial, intestinal microbiota was disturbed in 71.5 and 70% of cases of children of both groups. Upon reaching PCA 38-40 weeks in children from very early preterm birth, the frequency of detecting a violation of the microbial landscape increased 1.4 times, and in children from early preterm labor remained at the same level (100% and 75.8%, p = 0.005 in 1 -th and 2nd groups, respectively).

Thus, intestinal colonization by opportunistic microflora in all premature infants in the dynamics of the postnatal period was accompanied by an increase in the concentration of IFN-γ and IL-4, and a decrease in the content of IL-6 and IL-8 against the background of an increase in sIgA production in coprofiltrates. It indicates the development of humoral response and is confirmed by the presence of positive correlations between the level of sIgA in coprofiltrates at the age of 1 month of life and the content of IL-4 at 38-40 weeks of PCA.

It should be noted that an increase in the frequency of detecting a violation of the microbial landscape in children from very early preterm birth is apparently associated with a 4.5-fold decrease in the number of children breastfed by 38-40 weeks of PCA, in contrast to children from early preterm birth. A decrease in the content of sIgA in coprofiltrates in children with GA of 28-31 weeks indicates a reduced need for this immunoglobulin due to the elimination of microorganisms in 38-40 weeks of PCA compared with one month of age. The concentration of anti-inflammatory IL-4 in children from early preterm birth during this period practically did not change compared with one month of age, and in children from very early preterm birth it increased 1.4 times. It indicates the activation of humoral reactions in response to the introduction of conditional pathogenic microorganisms.

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Chapter IV. FEATURES OF THE FUNCTIONAL STATE OF THE IMMUNE SYSTEM OF NEWBORNS WITH BRONCHOPULMONARY DYSPLASIA

The problem of predicting outcomes in premature infants with ELBW remains relevant, which is due to both the lack of normative indicators and the absence of prognostic criteria that will allow differentiating various pathological conditions in the early postnatal period. It is not possible often to predict the severity and course of perinatal complications, since the clinical manifestations in a newborn may have a blurred picture and their delayed development.

As the survival rate of infants born with ELBW increased. BPD began to exert a significant influence on the prognosis of their health and life, with outcomes ranging from clinical recovery to high mortality (11–36%) in the first year of life [1].

According to modern authors, the "new" or post-surfactant form of BPD in very premature infants is characterized by a more favorable course [2, 3, 4, 5]. However, severe forms of the disease are more typical for children with extreme immaturity in the presence of concomitant risk factors [6].

According to the classification formulated in 2001 by A.H. Jobe, E.H. Bancalari, distinguish several degrees of BPD severity: mild - oxygen support up to 28 days of life and older and with its termination up to 36 weeks of postconceptional age (PCA); of moderate severity - oxygen support up to 28 days of life and older with FiO_2 <0.3 at 36 weeks of PCA; severe - the need for oxygen support at 36 weeks PCA with FiO_2> 0.3.

The development of complications (chronic and acute respiratory failure on the background of chronic, systemic arterial and pulmonary hypertension, osteoporosis, malnutrition, anemia) determine the severity and prognosis of BPD [7].

The incidence of BPD is higher in children with less birth weight and gestational age, which is confirmed by the results of various studies, for example, in deeply premature newborns with a birth weight of 500 to 750 grams, bronchopulmonary dysplasia is diagnosed in 35-67%, and in children from 1000 to 1500 grams does not exceed 3.6% of cases [8]. According to foreign authors, the frequency of BPD in very premature babies ranges from 29 to 49%, and in babies born at the time of very early preterm birth, it rises to 67% [9, 10, 11]. According to the studies of domestic authors, in newborns born at less than 32 weeks, a certain tendency towards a decrease in the incidence of BPD (15-30%) was noted, which is probably associated with the improvement of respiratory support and intensive care methods, as well as a change in diagnostic criteria. However, mortality in the first year of life remains quite high (11-36%) [12, 13].

By the time of discharge from the hospital, most of the children with severe BPD have concomitant diseases caused by perinatal damage to the central nervous

system, vision, hearing and other organs and systems, and by the age of one. They have psychomotor development disorders and constitute a risk group for the formation of obstructive pulmonary disease [6, 14, 15, 112].

This fact gives the BPD problem a great medical and social significance, which served as the purpose of studying the relationship between immunological parameters and the severity of the disease.

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4.1. Immunological reactivity of the immune system of children with bronchopulmonary dysplasia in the dynamics of the postnatal period

Depending on the outcome of the disease in 38-40 weeks of PCA and taking into account the gestational age (from very early and early preterm birth), children who subsequently developed BPD were subdivided into groups during the study.

Babies with BPD with GA of 22-27 weeks:

Group 1A - severe BPD, n = 17;

Group 1B - BPD of mild and moderate severity, n = 18;

1C group - without BPD, n = 7.

Children with BPD with GA of 28-31 weeks:

Group 2A - BPD of severe severity, n = 9;

Group 2B - BPD of mild and moderate severity, n = 24;

Group 2C - without BPD n = 9.

Studies have shown that all children who subsequently developed severe BPD, regardless of gestational age, had a lower body weight than children with mild to moderate degrees. At the same time, very premature infants with GA of 28-31 weeks with severe BPD had the lowest body weight (781.11 ± 158.6 g versus 909.08 ± 84.9 g and 951.22 ± 51.48 g). However, infants from very early prematurities had a lower gestational age (25.4 ± 1.53 versus 26.2 ± 0.88 weeks with mild to moderate BPD). No significant differences were found between the severity of BPD and the incidence of sepsis and pneumonia in children from very early prematurity. In children from early preterm birth, this pathology was almost 1.7

times more likely to be diagnosed in children with severe BPD than in children with mild and moderate BPD.

The etiology and pathogenesis of early anemia in premature infants are mainly determined by the physiological and biochemical characteristics of erythropoiesis and its regulation, as well as the gestational age of the child, since the most significant changes in hematopoiesis occur in the last 3 months of gestation [1]. It is known that the reserve fund of iron in premature infants is reduced and depends on the body weight at birth. Our studies have shown that anemia of prematurity was observed more often in children with ELBW of gestational age of 22-27 weeks. Moreover, severe anemia during the neonatal period in children with severe BPD, both from early and early preterm births, was 2.5 and 2.8 times more frequent than in children of the same gestational age with mild and moderate BPD, which required a greater number of repeated blood transfusions in newborns from very early preterm labor (4.3 ± 2.19 versus 2.2 ± 1.3 times, $p < 0.01$). In children with GA of 28-31 weeks and severe BPD, repeated blood transfusions were 2 times more frequent (2.7 ± 1.75 versus 1.3 ± 1.5 times in children with mild to moderate BPD). However, no significant differences were found.

When examining the umbilical cord blood of children with BPD who were born at the time of very early preterm labor, a significant increase in the absolute number of leukocytes was found (Table 31).

Absolute lymphocytosis was significantly more frequent in children with severe BPD. Also in this group of children, the content of lymphocytes (CD3 - $p_{1-2} = 0.047$, $p_{1-3} = 0.008$, CD4 - $p_{1-2} = 0.02$, $p_{1-3} = 0.05$, CD19 - $p_{1-2} = 0.02$, $p_{1-3} = 0.01$) and NK cells ($p_{1-2} = 0.05$, $p_{1-3} = 0.043$) significantly exceeded the indicators of children with mild and moderate BPD and children without BPD, which indicated activation of the B-cell link immunity and increased cytotoxic potential.

An increase in the number of regulatory cells with a receptor for IL-2, which is an activation marker ($CD25^+CD4^+$) ($p_{1-2} = 0.05$, $p_{2-3} = 0.05$) promotes the accelerated differentiation of regulatory lymphocyte populations and is the most important result of activation.

Table 31.

Population and subpopulation composition of umbilical cord blood lymphocytes from very early preterm labor that formed BPD, IU (P25-P75)

Indicators	Children of GA of 22-27 weeks			
	Group 1A (n=17)	**Group 1B (n=18)**	**Group 1C (n=7)**	**P**
Leukocytes, 10^9/l	7,0(6,4-12,0)	11,85(7,15-17,45)	5,0(3,78-6,4)	$_{1A-1C}$**=0,02** $_{1B-1C}$**=0,001**
Lymphocytes, %	68,5(56,25-73,0)	78,0(70,3-81,50)	71,0(65,0-75,0)	
Lymphocytes, 10^9/l	5,1(3,83-9,2)	3,44(3,09-3,69)	3,38(2,38-3,55)	$_{1A-1B}$**=0,015** $_{1A-1C}$ **=0,013**
CD3+, %	46,0(35,0-51,0)	38,0(35,0-69,0)	37,0(33,5-40,0)	
CD3+, 10^9/l	2,24(1,85-3,94)	1,42(1,31-1,78)	1,31(1,02-1,36)	$_{1A-1B}$=0,047 $_{1A-1C}$ **=0,008**
CD19+, %	12,0(7,0-19,0)	8,0(6,0-12,8)	12,0(8,5-130)	
CD19+, 10^9/l	1,06(0,25-1,46)	0,29 (0,22-0,44)	0,43(0,33-0,49)	$_{1A-1B}$ **=0,02** $_{1A-1C}$ **=0,01**
CD4+, %	31,0(24,0-38,0)	41,5(28,3-56,0)	23,0(18,0-25,5)	$_{1A-1B}$ **=0,01** $_{1B-1C}$ **=0,001**
CD4+, 10^9/l	1,7(0,8-2,3)	1,31(1,13-1,54)	0,78(0,63-0,93)	$_{1A-1B}$ **=0,014** $_{1B-1C}$ **=0,017**
CD8+, %	11,0(9,0-13,0)	15,5 (11,8-16,0)	9,0(7,5-13,5)	$_{1A-1B}$ =0,06 $_{1^B-1C}$ =0,048
CD8+, 10^9/l	0,54(0,3-1,34)	0,45(0,38-0,48)	0,28 (0,22-0,46)	
CD16+CD56+, %	8,0(4,0-10,0)	3(2,5-3,5)	2,0(2,0-3,0)	$_{1A-1B}$ =0,001 $_{1A-1C}$ =0,001
CD16+CD56+, 10^9/l	0,39(0,09-1,09)	0,11 (0,08-0,12)	0,09(0,06-0,12)	$_{1A-1B}$ =0,048 $_{1A-1C}$ =0,048
CD4/CD8	2,54(2,18-3,33)	3,43(2,91-4,15)	3,11(2,17-3,47)	
CD25/CD4+, %	3,0(2,0-5,0)	5,5(2,75-9,0)	2,0(1,0-3,0)	$_{1A-1B}$ **=0,05** $_{1B-1C}$ **=0,05**
CD25/CD4+, 10^9/l	0,19(0,06-0,25)	0,19(0,10-0,28)	0,09(0,03-0,11)	$_{1A-1C}$ **=0,01** $_{1B-1C}$ **=0,01**

Note: *p - the significance of differences between the groups of children (Mann-Whitney test): group 1A - children with severe BPD III degree, group 1B - children with mild and moderate BPD, group 1C - children without BPD.*

In children from early preterm birth, who formed and did not form BPD, the indicators of cellular immunity were comparable (Table 32).

Table 32.

Population and subpopulation composition of umbilical cord blood lymphocytes of children from early preterm birth formed BPD, UI (P25-P75)

Indicators	Children of GA of 28-31 weeks		
	Group 2A (n=9)	**Group 2B (n=25)**	**Group 2C (n=9)**
Leukocytes, 10^9/l	6,6 (4,7-6,9)	8,7 (6,05-12,5)	9,0(5,5-9,9)
Lymphocytes, %	75,5 (68,8-80,3)	69,0 (54,75-75,0)	65,5(60,5-70,5)
Lymphocytes, 10^9/l	3,6 (3,28-5,21)	3,77 (2,95-6,86)	7,49(5,5-14,43)
CD3+, %	47,0 (44,5-50,5)	43,5 (39,5-54,25)	37,0(35,0-45,5)
CD3+, 10^9/l	1,74 (1,43-2,15)	1,71 (1,23-3,19)	3,2(3,23-7,26)
CD19+, %	14 (10-23)	14 (9,25-17,25)	14(11,5-15)
CD19+, 10^9/l	0,47 (0,37-1,2)	0,59 (0,47-0,72)	0,83(0,59-2,86)
CD4+, %	33,0 (25,5-35,0)	32,5 (26,75-38,0)	21,0(18,5-31,0)
CD4+, 10^9/l	1,03 (0,95-1,5)	1,25 (0,92-2,42)	2,43(1,62-3,66)
CD8+, %	12,0 (10,5-16,5)	14,5 (11,5-11,75)	13(11-14)
CD8+, 10^9/l	0,6 (0,31-0,69)	0,58 (0,42-0,9)	0,89(0,69-1,82)
CD16+56+, %	7,0 (3,75-11,75)	5,5 (3,0-10,5)	6,0(5,5-9,0)
CD16+CD56+, 10^9/l	0,21 (0,08-0,35)	0,23 (0,09-0,59)	0,71(0,45-1,27)
CD4/CD8	3,08 (2,01-3,19)	2,07 (1,73-3,31)	1,78(1,7-2,26)
CD25+CD4+, %	4,0 (2,5-5,5)	4,0 (3,0-4,5)	2,5(1,75)4,0
CD25+CD4+, 10^9/l	0,18 (0,13-0,28)	0,14 (0,12-0,21)	0,3(0,15-0,54)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

By the end of the late neonatal period, an increase in the absolute number of T-cytotoxic CD8+ cells (p_{2-3} = 0.04) was observed at the level of a trend in the peripheral blood of children born at the time of very early preterm labor with mild and moderate BPD (Table 33).

Table 33.

Population and subpopulation composition of peripheral lymphocytes of premature babies at the age of 1 month of life, who formed BPD, IU (P25-P75)

Indicators	Children of GA of 22-27 weeks			
	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	P
Leukocytes, 10^9/l	10,9(9,8-14,1)	10,21(7,95-11,42)	8,15(7,63-9,64)	$_{1A-1C=}$0,06
Lymphocytes, %	50,5(43,75-58,0)	62,0(59,25-66,75)	60,0(58,0-63,0)	
Lymphocytes, 10^9/l	3,43(1,93-4,35)	4,42(3,35-6,12)	4,93(4,44-5,89)	$_{1A-1B=}$0,08 $_{1A-1C=}$0,03
CD3+, %	55(53-72)	54(48,5-67,0)	48(47-56)	
CD3+, 10^9/l	2,39(1,21-2,47)	2,12(1,56-3,14)	2,32(2,18-2,38)	
CD19+, %	22(14-30)	10(8-14)	16(13-17,5)	
CD19+, 10^9/l	0,26(0,22-0,5)	0,49(0,17-0,65)	0,77(0,57-0,81)	
CD4+, %	41(23-42)	39(28,5-48,5)	40(37-44,5)	
CD4+, 10^9/l	1,82(0,37-1,83)	1,24(1,18-2,21)	1,79(1,65-1,86)	
CD8+, %	21(20-28)	17(14,5-24)	14(11-16)	
CD8+, 10^9/l	0,72(0,54-0,83)	0,94(0,55-1,16)	0,62(0,50-0,64)	$_{1B-1C=}$**0,04**
CD16+CD56+, %	17(10-18)	10(7-15,5)	11(10,5-11,0)	
CD16+CD56+, 10^9/l	0,44(0,27-0,46)	0,43(0,27-0,82)	0,48(0,44-0,49)	
CD4/CD8	2,1(0,44-2,52)	2,15(1,11-2,93)	2,72(2,57-3,86)	
CD25+CD4+, %	4(4-5)	6(4-7)	6(5,5-6,5)	
CD25+CD4+, 10^9/l	0,17(0,08-0,19)	0,21(0,17-0,42)	0,29(0,24-0,30)	

Note: *p - the significance of differences between groups of children (Mann-Whitney test): group 1A - children who have formed severe BPD III degree, group 1B - children who have formed BPD mild and moderate degree, group 1C - children without BPD.*

In newborns with GA of 28-31 weeks, no significant differences in the parameters of the cellular component of immunity were found (Table 34).

Table 34.

Population and subpopulation composition of peripheral lymphocytes of premature babies at the age of 1 month of life, who formed BPD, IU (P25-P75)

Indicators	Children of GA of 28-31 weeks		
	Group 2A (n=9)	Group 2B (n=25)	Group 2A (n=9)
Leukocytes, 10^9/l	6,6(4,7-6,9)	8,7(6,05-12,5)	9,0(5,5-9,9)
Lymphocytes, %	75,5(68,8-80,3)	69,0(54,75-75,0)	65,5(60,5-70,5)
Lymphocytes, 10^9/l	3,6(3,28-5,21)	3,77(2,95-6,86)	7,49(5,5-14,43)
CD3+, %	47,0(44,5-50,5)	43,5(39,5-54,25)	37,0(35,0-45,5)
CD3+, 10^9/l	1,74(1,43-2,15)	1,71(1,23-3,19)	3,2(3,23-7,26)
CD19+, %	14(10-23)	14(9,25-17,25)	14(11,5-15)
CD19+, 10^9/l	0,47(0,37-1,2)	0,59 (0,47-0,72)	0,83(0,59-2,86)
CD4+, %	33,0(25,5-35,0)	32,5(26,75-38,0)	21,0(18,5-31,0)
CD4+, 10^9/l	1,03(0,95-1,5)	1,25(0,92-2,42)	2,43(1,62-3,66)
CD8+, %	12,0(10,5-16,5)	14,5(11,5-11,75)	13(11-14)
CD8+, 10^9/l	0,6(0,31-0,69)	0,58(0,42-0,9)	0,89(0,69-1,82)
CD16+CD56+, %	7,0(3,75-11,75)	5,5(3,0-10,5)	6,0(5,5-9,0)
CD16+CD56+, 10^9/l	0,21(0,08-0,35)	0,23(0,09-0,59)	0,71(0,45-1,27)
CD4/CD8	3,08(2,01-3,19)	2,07(1,73-3,31)	1,78(1,7-2,26)
CD25+CD4+, %	4,0(2,5-5,5)	4,0(3,0-4,5)	2,5(1,75)4,0
CD25+CD4+, 10^9/l	0,18(0,13-0,28)	0,14(0,12-0,21)	0,3(0,15-0,54)

Note. *The significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

An increased content of NK cells remained (p_{1-3} = 0.01) by 38-40 weeks of PCA in the peripheral blood of children born at the time of very early preterm labor who developed severe BPD, which is associated with the transferred infectious-inflammatory diseases (Table 35).

Table 35.

Population and subpopulation composition of peripheral blood lymphocytes of premature infants with BPD in 38-40 weeks of PCA, IU (P25-P75)

Indicators	Children of GA of 22-27 weeks			
	Group 1A (n=17)	Group1B (n=18)	Group 1A (n=17)	P
Leukocytes, 10^9/l	8,6(7,7-8,95)	7,11(5,57-8,54)	6,71(6,48-7,57)	
Lymphocytes, %	69,0(54,5-73,8)	68,5(64,8-79,3)	61,5(58,5-65,25)	
Lymphocytes, 10^9/l	4,19(3,24-4,74)	4,54(4,12-5,18)	4,32(3,95-4,67)	
CD3+, %	48,5(35,0-60,5)	50,0(45,5-55,0)	60,0(57,5-64,5)	$_{1A-1C=}$0,04
CD3+, 10^9/l	1,74(1,52-2,53)	2,05(1,75-2,87)	2,36(2,32-2,41)	**$_{=}^{1A-1C}$0,025**
CD19+, %	34,0(18,0-38,75)	28,0(17,5-30,0)	20,0(16,0-23,5)	
CD19+, 10^9/l	1,07(0,49-1,48)	1,24(0,6-1,53)	0,68(0,6-0,91)	
CD4+, %	29,0(26-36)	34(24-37)	44(38,5-47)	
CD4+, 10^9/l	1,05(0,84-1,57)	1,44(1,13-1,72)	1,71(1,63-1,76)	**$_{=}^{1A-1C}$0,010**
CD8+, %	19,5(13,5-25,5)	15,0(12,5-20,5)	18,0(17,5-22,0)	
CD8+, 10^9/l	0,61(0,43-0,94)	0,67(0,53-0,78)	0,70(0,66-0,75)	
CD16+CD56+, %	22,0(10,5-24,5)	12,0(8,5-16,5)	8,5(7,3-10,0)	**$_{=}^{1A-1C}$0,010**
CD16+CD56+, 10^9/l	0,53(0,29-0,91)	0,58(0,33-0,68)	0,31(0,28-0,44)	
CD4/CD8	1,81(0,94-2,39)	2,11(1,65-2,5)	2,7(2,6-2,75)	
CD25+CD4+, %	4,5(3,3-5,0)	4,0(3,75-5,3)	5,0(4,8-5,25)	
CD25+CD4+, 10^9/l	0,19(0,11-0,24)	0,18(0,15-0,23)	0,19(0,18-0,21)	

Note: *p - the significance of differences between groups of children (Mann-Whitney test): group 1A - children who have formed severe BPD III degree, group 1B - children who have formed BPD mild and moderate, group 1C - children without BPD.*

A decrease in the absolute and relative number of CD3 cells of the 1st group (p_{1-3} = 0.04, p_{1-3} = 0.03) testified to the insufficiency of the cellular effector link of immunity, and a decrease in CD4 lymphocytes (p_{1-3} = 0, 01) - disruption of the regulatory link of immunity.

In children from early preterm labor with severe BPD, there was an increase in the number of leukocytes, and at the level of the trend in the percentage of CD16+CD56 + lymphocytes, no changes were found in other parameters of cellular immunity (Table 36).

Table 36.

Population and subpopulation composition of peripheral blood lymphocytes of premature infants with BPD in 38-40 weeks of PCA, IU (P25-P75)

Indicators	Children of GA of 28-31 weeks			
	Group 2A (n=9)	**Group 2B (n=25)**	**Group 2A (n=9)**	**P**
Leukocytes, 10^9/l	9,2 (8,59-9,8)	6,78(6,4-8,63)	7,19(6,5-8,7)	$_{2A-2B}$**=0,025** $_{2B-2C}$ **=0,03**
Lymphocytes, %	73,5 (65,75-80,0)	67,0 (60-69,75)	79 (71-79)	
Lymphocytes, 10^9/l	5,62 (4,37-7,07)	4,65 (4,05-4,84)	5,14 (4,44-5,61)	
CD3+, %	51,0 (44,25-53,75)	49,0 (43,25-52,75)	50 (50-51)	
CD3+, 10^9/l	2,35 (2,27-2,73)	2,11 (1,8-2,41)	2,62 (2,47-2,64)	
CD19+, %	30,5 (27,25-34,75)	27,5 (19,5-34,0)	25,0 (22,0-29,0)	
CD19+, 10^9/l	1,87 (1,23-2,56)	1,23 (0,85-1,49)	1,13 (1,11-1,8)	
CD4+, %	32,5 (24,5-38,75)	33,5 (28,75-38,5)	37 (32-43)	
CD4+, 10^9/l	1,74 (1,52-1,93)	1,44 (1,3-1,7)	1,91 (1,63-2,21)	
CD8+, %	14,0 (11,5-18,5)	13,5 (13,0-18,5)	15 (12-18)	
CD8+, 10^9/l	0,81 (0,5-1,33)	0,62 (0,59-0,76)	0,78 (0,6-0,8)	
CD16+CD56+, %	17,0 (14,5-19,25)	13,5 (10,0-15,0)	12,0 (7,0-12)	$_{2A-2C}$ **=0,073**
CD16+CD56+, 10^9/l	1,01 (0,63-1,4)	0,63 (0,34-0,69)	0,62 (0,31-0,72)	
CD4/CD8	2,08 (1,08-3,41)	2,17 (1,88-2,38)	3,08 (1,77-3,2)	
CD25+CD4+, %	4,0 (3,0-5,5)	5(5-6)	4(4-5)	
CD25+CD4+, 10^9/l	0,23 (0,22-0,25)	0,24 (0,20-0,29)	0,20 (0,18-0,26)	

Note: *p - the level of significance of differences between groups of children (Mann-Whitney test): group 2A - children with severe BPD of III degree, group 2B - children who have formed BPD of mild and moderate degree, group 2C - children without BPD.*

When assessing the intracellular cytokines of the umbilical cord blood, there were no significant differences between the compared groups of children (Tables 37, 38)

Table 37.

Levels of intracellular cytokines in the umbilical cord blood of premature infants who have formed BPD, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)
$CD4^+CD3+IFN-\gamma$ self-existing, %	2,9(1,36-4,13)	2,31(1,74)	3,95(2,51-8,03)
$CD4^+IFN-\gamma$ suscitate, %	3,83(2,86-6,17)	4,49(2,61-6,5)	4,58(2,52-6,0)
$CD4^+IL-4$ self-existing, %	2,47(1,32-3,06)	1,69(0,77-3,94)	0,9(0,9-1,38)
$CD4^+IL-4$ suscitate, %	3,84(2,43-5,7)	4,59(2,73-5,01)	4,9(3,35-4,9)
$CD4^+IFN-\gamma^+$ / $CD4^+IL-4^+$ self-existing, c.u.	1,36(1,28-1,72)	1,54(1,28-1,75)	1,26(1,21-1,27)
$CD4^+IFN-\gamma^+$ / $CD4^+IL-4^+$ suscitate, c.u.	1,8(1,04-1,54)	1,16(0,97-1,51)	1,22(1,21-1,3)

Note. *The level of significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Table 38.

Levels of intracellular cytokines in the umbilical cord blood of premature infants who have formed BPD, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)
$CD4^+CD3+IFN-\gamma$ self-existing, %	3,59 (2,85-5,04)	3,18 (2,78-4,5)	5,82 (1,89-6,09)
$CD4^+IFN-\gamma^+$ suscitate, %	5,44 (4,63-6,11)	3,96 (2,35-7,67)	6,5 (4,58-9,06)
$CD4^+IL-4^+$ self-existing, %	3,04 (0,82-4,32)	1,25 (0,82-3,17)	2,28 (0,78-2,5)
$CD4^+IL-4^+$ suscitate, %	3,22 (2,88-4,5)	2,95 (2,22-3,8)	3,6 (2,6-4,32)
$CD4^+IFN-\gamma^+$ / $CD4^+IL-4^+$ self-existing, c.u.	2,04 (,184-3,13)	2,42 (1,37-2,65)	2,55 (1,43-2,8)
$CD4^+IFN-\gamma^+$ / $CD4^+IL-4^+$ suscitate, c.u	1,58 (1,32-1,84)	1,14 (0,64-2,05)	1,9 (1,68-2,1)

Note. *The level of significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

When assessing the intracellular cytokines of the peripheral blood of children of all groups, no significant differences were found (Tables 39, 40).

Table 39.

Intracellular cytokine levels in premature infants with BPD at 1 month of life, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	2,5(1,22-4,56)	1,93(1,24-3,91)	3,87(3,4-5,59)
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	3,55(2,51-5,05)	3,39(2,23-4,25)	7,84(6,2-10,18)
$CD4^+IL\text{-}4^+$ self-existing, %	1,79(0,91-3,12)	1,55(1,02-2,44)	2,73(2,6-2,95)
$CD4^+IL\text{-}4^+$ suscitate, %	2,71(1,7-3,49)	2,18(1,68-3,29)	3,28(3,1-4,81)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,36(1,26-1,62)	1,29(1,15-1,46)	1,42(1,37-1,45)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,63(1,52-2,45)	1,64(1,46-2,14)	2,21(1,86-2,57)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Table 40.

Intracellular cytokine levels in premature infants with BPD at 1 month of life, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)
$CD4^+CD3+IFN\text{-}\gamma$ self-existing, %	1,71(1,1-2,37)	2,31(1,19-4,27)	2,56(2,09-3,2)
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	4,71(2,61-7,52)	5,19(2,43-6,66)	5,24(4,45-6,5)
$CD4^+IL\text{-}4^+$ self-existing, %	1,12(0,89-2,41)	1,14(1,03-2,12)1,9	1,14-2,34()
$CD4^+IL\text{-}4^+$ suscitate, %	2,93(1,28-3,02)	3,67(2,23-4,73)	4,04(3,55-4,5)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,57(1,36-1,73)	1,68(1,39-1,98)	1,81(1,36-2,07)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,59(1,33-2,06)	1,24(1,08-1,33)	1,46(1,19-4,24)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Analysis of intracellular cytokines showed that upon reaching 38-40 weeks of PCA, an increased number of $CD4^+IL\text{-}4^+$ cells in the stimulated test was observed in children who developed BPD regardless of severity ($p_{1-3} = 0.06$, $p_{2-3} = 0.03$) (Tables 41, 42).

Table 41.

Intracellular cytokine levels in premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	p
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	2,6(1,93-4,07)	3,08(1,27-4,05)	4,29(3,35-4,87)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	5,63(4,82-6,44)	6,91(2,02-12,87)	6,1(6,0-7,49)	
$CD4^+IL\text{-}4^+$ self-existing, %	1,32(2,25-3,2)	1,43(0,9-3,2)	3,2(2,26-4,23)	
$CD4^+IL\text{-}4^+$ suscitate, %	2,22(2,01-3,21)	4,6(2,28-10,17)	5,9(4,95-6,05)	**$P_{1-3=}$0,06 $P_{2-3=}$0,03**
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,54(1,27-1,61)	1,37(1,23-1,82)	1,46(1,25-1,64)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	2,45(2,1-3,01)	1,38(1,15-1,91)	1,43(1,27-2,48)	**$P_{1-3=}$0,045**

Note: *p - significance of differences between groups of children (Mann-Whitney test): group 1A - children with severe BPD of III degree, group 1B - children with BPD of mild and moderate degree, group 1C - children without BPD.*

Table 45c

In all premature infants with severe BPD, the cell polarization index had a pro-inflammatory orientation, which is associated with antigenic stimulation with bacterial agents ($p_{1-3} = 0.045$, $p_{4-6} = 0.09$).

Table 42.

Intracellular cytokine levels in premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)	p
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	2,37(2,26-3,68)	2,6(2,05-4,61)	3,81(2,45-4,19)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	3,3(3,01-3,88)	3,58(2,58-5,54)	4,72(3,67-5,64)	
$CD4^+IL\text{-}4^+$ self-existing, %	1,19(1,02-1,41)	1,25(0,98-2,33)	1,91(1,4-2,3)	
$CD4^+IL\text{-}4^+$ suscitate, %	3,53(2,95-3,79)	3,62(2,53-5,26)	4,06(3,77-4,37)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,82(1,72-1,93)	1,8(1,59-2,03)	1,66(1,43-1,74)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,3(0,08-1,54)	1,04(0,93-1,93)	1,09(1,0-3,84)	**P_{4-6}=0,09** **P_{5-6}=0,06**

Note: *p - significance of differences between groups of children (Mann-Whitney test): group 2A - children who have formed severe BPD of III degree, group 2B - children who have formed BPD of mild and moderate degree, group 2C - children without BPD.*

Thus, in all children with mild and moderate BPD, regardless of gestational age, there were no significant differences in the population composition of lymphocytes in the dynamics of the postnatal period in comparison with the indicators of children without BPD. Nevertheless, in children from very early preterm birth, an increase in the absolute number of leukocytes and the level of expression of the $CD4^+CD25^+$ receptor at birth was recorded.

The greatest changes were noted in the indices of adaptive immunity during the formation of severe BPD in children with 22-27 weeks of GA. It was characterized by activation of the cellular link of the immune system, manifested by an increase in T- and B-lymphocytes, T-helpers, CD16+CD56+ cells and regulatory $CD4^+CD25^+$ lymphocytes with absolute leuko- and lymphocytosis at birth. Maintaining a high level of leukocytes and NK-cells, with a decrease in the number of T-lymphocytes and T-helpers - according to 38-40 weeks of GA. In children of gestational age of 28-31 weeks, regardless of the severity of BPD, there were no significant differences in the indicators of adaptive immunity.

The first line of defense against foreign pathogens is innate immunity, which is the earliest defense mechanism in evolutionary terms and on response time. Preactivation of innate immunity triggers adaptive responses. The implementation of innate immune responses is carried out through many types of cells. Cells of the

myeloid series are a kind of effectors of innate immunity. Monocytes are the main component of the myeloid cell pool. The cells that cause congenital resistance - phagocytes in premature newborns are characterized by reduced activity.

The transferrin receptor (CD71+) is a marker of early activation, and an increase in its expression level was observed on proliferating umbilical cord blood monocytes in children with 22-27 weeks of GA (p_{1-2} = 0.012) (Table 43).

Table 43.

Markers of activation of umbilical cord blood monocytes in children from very early preterm labor, which formed BPD, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	P
CD11b+CD14+, %	20,0(15-36)	65,5(38,25-68)	21,5(10,5-45,25)	
CD11b+CD14+, abs.	0,13(0,07-0,16)	0,11(0,06-0,4)	0,08(0,03-0,13)	
CD64+CD14+, %	17,5(7,75-38,25)	17(12-32)	28,5(20,25-36,75)	
CD64+CD14+, 10^9/l	0,09(0,04-0,22)	0,05(0,04-0,15)	0,29(0,16-0,41)	
CD14+HLA-DR+, %	23,0(14,25-29,0)	21(10-61)	11(7-22)	
CD14+HLA-DR+, 10^9/l	0,10(0,09-0,31)	0,05(0,04-0,13)	0,06(0,04-0,19)	
CD71+CD14+, %	18(16,5-20,5)	11,0(7,75-15,5)	10,0(8,75-14,0)	$_{1A-1C}$**=0,012**
CD71+CD14+, 10^9/l	0,15(0,05-0,22)	0,03(0,03-0,04)	0,02(0,02-0,09)	$_{1A-1C}$**=0,012**

Note: *p - significance of differences between groups of children (Mann-Whitney test): group 1A - children with severe BPD III degree, group 1B - children with mild and moderate degree of BPD, group 1C - children without BPD.*

In children with 28-31 weeks of GA with BPD, a statistically significant increase in the percentage of CD14/HLA-DR (p_{2A-2C} = 0.01, p_{2B-2C} = 0.023) was found in indicators of innate immunity of newborns, which, according to some authors, correlates with an increase risk of infectious pathology (Table 44).

Postponed sepsis in the neonatal period was observed in newborns who subsequently developed BPD in 23.6% (17 of 72 children). Correlation analysis revealed a strong positive relationship between the amount of CD14+HLA-DR+ in cord blood with the development of sepsis in children born at the time of early preterm labor (r = 0.73, p = 0.004) and the formation of a severe form of BPD (r = 0, 52, p = 0.018).

Table 44.

Markers of activation of umbilical cord blood monocytes in children from early preterm labor that formed BPD, ME (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)	P
CD11b+CD14+, %	39,0(30,5-60,0)	46,0(35,0-51,0)	21,0(15,0-27,0)	
CD11b+CD14+, abs.	0,16(0,10-0,25)	0,23(0,15-0,39)	0,06(0,06-0,07)	
CD64+CD14+, %	17,5(13,25-25,5)	42,0(38,0-44,0)	35(29,5-37,5)	
CD64+CD14+, 10^9/l	0,06(0,05-0,06)	0,19(0,09-0,32)	0,15(0,11-0,16)	
CD14+HLA-DR+, %	58(34-64,5)	33(21-47,5)	14(13-19,5)	
CD14+HLA-DR+, 10^9/l	0,16(0,10-0,29)	0,20(0,14-0,27)	0,07(0,06-0,07)	$_{2A-2C}$**=0,010** $_{2B-2C}$**=0,023**
CD71+CD14+, %	17(14,5-24,0)	14(11,75-18,25)	16,0(14,25-22,5)	$_{2B-2C}$**=0,023**
CD71+CD14+, 10^9/l	0,07(0,05-0,10)	0,10(0,08-0,12)	0,12(0,10-0,14)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 2A - children with severe BPD of III degree, group 2B - children who have formed BPD of mild and moderate degree, group 2C - children without BPD.*

A significant decrease in the absolute and relative amount of CD14/HLA-DR was revealed when comparing indicators of innate immunity of newborns from very early preterm birth, regardless of the severity of BPD. The number of $CD14^+CD64^+$ cells was reduced only in children with a severe form of the disease ($p_{1-3} = 0.01$, $p_{2-3} = 0.01$) (Table 45), which is associated with a high percentage of cases of infectious and inflammatory diseases in this group. (pneumonia - in 100% of cases).

Table 45.

Markers of activation of peripheral blood monocytes of premature infants at 1 month of life, who have formed BPD, ME (P25-P75)

Indicators	1A group (n=17)	1B group (n=18)	1C group (n=7)	P
CD11b+CD14+, %	65(59-67)	50(48-58,75)	71(66,25-76,25)	
CD11b+CD14+, abs.	0,85(0,76-1,07)	0,97(0,91-1,03)	0,74(0,58-0,87)	
CD64+CD14+, %	17,5(13,8-22,5)	39(20,3-55,0)	41(22-60)	**$P_{A-C=}$0,007 P_{A-B}=0,004**
CD64+CD14+, 10^9/l	0,15(0,05-0,24)	0,31(0,28-0,48)	0,53(0,28-0,79)	**P_{A-B}=0,04 P_{A-C}=0,07**
CD14+HLA-DR+, %	64(59-69)	65(44,5-77)	84(76,5-87,5)	**$P_{A-C=}$0,01 $P_{B-C=}$0,01**
CD14+HLA-DR+, 10^9/l	0,88(0,79-0,92)	0,9(0,67-0,97)	1,45(1,05-1,56)	**$P_{A-C=}$0,06**
CD71+CD14+, %	8(7-16)	14(6-18)	12(8-49,5)	
CD71+CD14+, 10^9/l	0,13(0,10-0,22)	0,11(0,07-0,24)	0,11(0,09-0,85)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 1A - children with severe BPD III degree, group 1B - children with mild and moderate BPD, group 1C - children without BPD.*

In children with at 28-31 weeks of GA, no significant differences were found in the indicators of the monocytic link of immunity (Table 46).

Table 46.

Activation markers of peripheral blood monocytes in premature infants at 1 month of age, who have formed BPD, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)
CD11b+CD14+, %	60(59-63)	79(66-82)	64(58,5-69)
CD11b+CD14+, 10^9/l	0,63(0,53-0,68)	0,46(0,32-0,49)	0,49(0,43-0,54)
CD64+CD14+, %	15(10-20)	30(18,75-51)	56(36-60)
CD64+CD14+, 10^9/l	0,17(0,13-0,22)	0,22(0,06-0,34)	0,43(0,27-0,47)
CD14+HLA-DR+, %	81,0(58,5-66,5)	67,5(50,5-76,0)	67,0(59,0-69,0)
CD14+HLA-DR+, 10^9/l	0,53(0,43-0,73)	0,56(0,44-0,72)	0,57(0,40-0,80)
CD71+CD14+, %	8,0(5,25-16,75)	15,0(8,0-20,23)	12(11-25)
CD71+CD14+, 10^9/l	0,10(0,04-0,16)	0,11(0,07-0,22)	0,16(0,09-0,30)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

When conducting a correlation analysis, it was found that a reduced content of CD14+HLA-DR+ monocytes in children with ELBW, born at the time of very early preterm labor, positively correlated with the presence of pneumonia at the age of 1 month of life (r = 0.48, p = 0.03).

In the study of markers of activation of peripheral blood monocytes in newborns from very early preterm labor, which subsequently formed a severe BPD, a decrease in $CD64^{+}CD14^{+}$ (p_{1-2} = 0.01, p_{1-3} = 0.03) was noted in comparison with the indicators of children with mild and the average degree and children without BPD of the same gestational age (Table 45a). The relative number of CD14+HLA-DR+ monocytes in all children with BPD was reduced at the level of the tendency (p_{1-3} = 0.067, p_{2-3} = 0.07) to at 38-40 weeks of PCA (Tables 47, 48).

Table 47.

Markers of peripheral blood monocyte activation in premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	P
CD11b+CD14+, %	77(75-78,5)	75,5(73,8-77,3)	75(67,5-77,5)	
CD11b+CD14+, abs.	0,50(0,39-0,58)	0,51(0,38-0,64)	0,41(0,33-0,47)	
CD64+CD14+, %	27(16,3-42,5)	50(35,3-65,0)	63,5(47,5-73,3)	**$P_{1A-1B=}$0,010** **$P_{1A-1C=}$0,03**
CD64+CD14+, 10^9/l	0,24(0,12-0,27)	0,27(0,12-0,41)	0,23(0,22-0,45)	
CD14+HLA-DR+, %	70,5(62,5-78,5)	74,0(64,8-83,0)	80,5(78,15-82,0)	**$P_{1A-1C=}$0,067** **$P_{1B-1C=}$0,07**
CD14+HLA-DR+, 10^9/l	0,49(0,39-0,56)	0,46(0,35-0,60)	0,4(0,38-0,57)	
CD71+CD14+, %	18(13-23)	13(9,5-15,5)	19(17-21)	
CD71+CD1, 10^9/l	0,12(0,07-0,22)	0,08(0,05-0,011)	0,12(0,10-0,14)	

Note: *p - significance of differences between groups of children (Mann-Whitney test): group 1A - children who have formed severe BPD III degree, group 1B - children who have formed BPD of mild and moderate degree, group 1C - children without BPD.*

Table 48.

Markers of peripheral blood monocyte activation in premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)
CD11b+CD14+, %	83,5(81,12-85,8)	81,5(78,25-84,75)	86(84-88)
CD11b+CD14+, abs.	0,9(0,8-1,0)	0,38(0,30-0,46)	0,72(0,64-0,80)
CD64+CD14+, %	80(72,5-83,5)	78(64,5-82,5)	75(70-80)
CD64+CD14+, 10^9/l	0,58(0,58-0,63)	0,38(0,30-1,76)	0,50(0,47-0,52)
CD14+HLA-DR+, %	82,5(70,5-90,25)	73,0(63,25-78,75)	76(74-78)
CD14+HLA-DR+, 10^9/l	0,87(0,71-0,98)	0,58(0,34-0,74)	0,81(0,59-0,87)
CD71+CD14+, %	15,5(12,0-26,5)	12,0(9,25-19,5)	15,0(8,0-16,0)
CD71+CD14+, 10^9/l	0,19(0,14-0,27)	0,13(0,06-0,19)	0,12(0,11-0,14)

Note. *The significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

When studying the level of cytokines in the serum of umbilical cord blood, in children with 22-27 weeks of GA, who subsequently formed BPD, regardless of the severity of this pathology, there was a significant increase in the level of IL-6 and IL-8 (Table 49).

Table 49.

Levels of umbilical cord blood cytokines in children from very early preterm labor that formed BPD, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	P
IFN- γ, pg/ml	12,23(9,72-13,9)	12,14(11,34-13,6)	10,42 (8,13-10,73)	
IL-6, pg/ml	120,43(12,6-160,78)	110,3(20,75-166,05)	16,5 (12,01-61,15)	$_{1A-1C}$**=0,03** $_{1B-1C}$**=0,05**
IL-8, pg/ml	85,32(70,76-120,8)	131,1(79,42-172,4)	46,32 (39,03-53,29)	$_{1A-1C}$**=0,015** $_{1B-1C}$**=0,015**
IL-4, pg/ml	0,74(0,48-0,87)	0,48(0,22-0,8)	0,61 (0,42-0,84)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 1A - children who have developed severe BPD III degree, group 1B - children who have formed BPD of mild and moderate degree, group 1C - children without BPD.*

Apparently, this is due to the fact that these mediators are markers of the development of the inflammatory process, an increase in the serum of the umbilical cord blood may be due to the presence of the transferred hypoxia, intrauterine infection. In children from early preterm labor, the concentration of IL-6 was comparable to the indicators of children without BPD, and the level of IL-8 significantly exceeded the indicators of children in the 1C group (Table 50).

Table 50.

Levels of umbilical cord blood cytokines in children from early preterm labor that formed BPD, IU (P25-P75)

Indicators	Group 2A (n=17)	Group 2B (n=18)	Group 2C (n=7)	P
IFN- γ, pg/ml	8,11(4,06-10,09)	1,07(0,54-7,85)	11,22(11,03-11,4)	
IL-6, pg/ml	4,44(3,84-12,49)	5,86(4,07-13,81)	14,85(3,37-21,83)	
IL-8, pg/ml	126,16(25,9-272,0)	24,37(13,6-47,13)	25,9(19,1-37,94)	$_{2A-2C}$**=0,003** $_{2A-2B}$**=0,003**
IL-4, pg/ml	0,93(0,49-1,13)	0,61(0,52-0,96)	0,93(0,71)0,95	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 2A - children who have developed severe BPD III degree, group 2B - children who have formed BPD of mild and moderate degree, group 2C - children without BPD.*

By the end of the neonatal period, the content of IL-8 in children who developed BPD decreased 2.8 and 4.8 times relative to the initial level (Tables 51, 52), but remained relevantly significant compared to newborns without BPD, probably at this stage of the examination may be a consequence of pneumonia suffered at birth (35.3% and 27.8%).

Table 51.

Levels of peripheral blood serum cytokines in premature infants at 1 month of age who subsequently formed BPD, IU (P25-P75)

Indicators	Group 1A (n=17)	Group 1B (n=18)	Group 1C (n=7)	P
IFN- γ, pg/ml	2,21(1,1-3,87)	3,77 (0,28-13,12)	2,7(0,0-5,93)	
IL-6, pg/ml	4,69(4,35-10,29)	5,63(4,88-6,12)	5,1(4,2-5,94)	
IL-8, pg/ml	30,63(21,25-41,42)	27,07(25,56-31,33)	15,8(12,35-18,75)	$_{1A-1C=}$**0,010** $_{1B-1C=}$**0,03**
IL-4, pg/ml	1,39(0,73-2,66)	1,74(1,42-1,79)	0,0(0,0-1,13)	

Note: *p - significance of differences between groups of children (Mann-Whitney test): group 1A - children with severe BPD of III degree, group 1B - children with BPD of mild and moderate degree, group 1C - children without BPD.*

Table 52.

Levels of peripheral blood serum cytokines in premature infants at 1 month of age who subsequently formed BPD, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)	P
IFN- γ, pg/ml	3,32(2,77-5,56)	2,21(0,83-4,44)	1,38(0,0-4,43)	
IL-6, pg/ml	3,04(2,46-35,08)	7,76(5,2-18,48)	4,95(3,08-8,5)	
IL-8, pg/ml	57,68(36,53-72,96)	19,77(15,96-25,44)	12,77(10,49-13,67)	$_{2A-2B}$=0,012 $_{2A-2C}$=0,010 $_{2B-2C}$=0,010
IL-4, pg/ml	0,65(0,33-1,51)	1,96(1,91-2,05)	1,95(1,9-1,99)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 2A - children who have developed severe BPD III degree, group 2B - children who have formed BPD of mild and moderate degree, group 2C - children without BPD.*

A study of pro- and anti-inflammatory cytokines in peripheral blood serum showed that in all premature infants, regardless of gestational age, there were no significant differences in BPD (Tables 53, 54).

Table 53.

Levels of cytokines in the peripheral blood of premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group1A (n=17)	Group 1B (n=18)	Group 1C (n=7)
IFN- γ, pg/ml	1,1(0,96-1,52)	0,0 (0,0-9,65)	0,0(0,0-0,9)
IL-6, pg/ml	3,91(3,77-4,8)	3,78(2,46-4,35)	2,75(2,36-2,97)
IL-8, pg/ml	16,72(10,75-31,18)	13,2(12,99-25,4)	15,5(12,8-17,75)
IL-4, pg/ml	2,7(2,1-2,93)	1,82(1,72-2,1)	20,5(1,892,7)

Note. *The significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Table 54.

Levels of cytokines in the peripheral blood of premature infants with BPD at 38-40 weeks of PCA, IU (P25-P75)

Indicators	Group 2A (n=9)	Group 2B (n=25)	Group 2C (n=9)
IFN- γ, pg/ml	0,55(0,55-2,21)	3,32(0,0-4,71)	8,95(1,66-9,51)
IL-6, pg/ml	6,45(5,08-13,48)	5,39(2,93-11,27)	6,72(2,75-13,45)
IL-8, pg/ml	13,54(11,87-17,73)	23,48(11,53-34,06)	13,47(12,9-80,54)
IL-4, pg/ml	1,6(1,57-1,91)	2,1(2,0-2,4)	2,46(2,4-2,48)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Thus, it was found in the study of indicators of innate immunity that despite the increased level of proliferation of $CD14^+CD71^+$ monocytes at birth in children from very early preterm birth with severe BPD, which in the postnatal period of a child's life can have an anti-inflammatory effect [2]. A significant a decrease in the functional activity of monocytes according to the presentation of infectious pathogens of lymphocytes ($CD14^+HLA\text{-}DR^+$) in children with GA of 22-27 weeks with BPD at the age of 1 month of life and a decrease at the level of the tendency towards the outcome of the disease at 38-40 weeks of PCA were observed. It also indicates the past infectious pathology, most often detected in these children. According to Kanakoudi-Tsakalidou, the HLA-DR expression on monocytes may be critical in the presence of respiratory distress syndrome [3]. In addition, according to F. Genel et al. (2010), a decrease in the HLA-DR expression on circulating monocytes in newborns with sepsis was observed [4]. According to the results of a study by other authors, no significant differences were found in the HLA-DR expression by monocytes in infected and uninfected infants, as well as among healthy children [5]. Our study found a strong positive relationship between the level of CD14/HLA-DR in cord blood with the development of sepsis in children born at the time of early preterm labor ($r = 0.73$, $p = 0.004$) and the formation of a severe form of BPD ($r = 0, 52$, $p = 0.018$).

Currently, the role of adhesive molecules in the pathogenesis of respiratory disorders is being actively studied. There was a decrease in the number of $CD14^+CD64^+$ monocytes in children from very early preterm birth with severe BPD, both with the development of an active form of the disease and its outcome. It indicates a decrease in intracellular absorption opsonized microbes and is consistent with literature sources [6].

There are data on the formation of BPD as a result of an imbalance of pro-inflammatory and anti-inflammatory mechanisms, highlighting a large role for pro-inflammatory cytokines [7, 8] and emphasizing the insufficient activity of anti-inflammatory ones.

Evaluation of the cytokine status showed that during the formation of BPD, regardless of the severity of this disease, increased production of IL-8 was noted in children from very early preterm birth during the neonatal period, in children with GA of 28-31 weeks - at the age of 1 month of life. A high level of IL-6 at birth was recorded only in children with GA of 22-27 weeks, which is due to infectious and inflammatory diseases in the neonatal period (sepsis, pneumonia), deaths in this group of children and is consistent with literature data. A number of foreign authors associate high levels of IL-6 in umbilical cord blood with an increased risk of morbidity and mortality in the newborn [9, 10], with RDS-associated inflammation and early peri / intraventricular hemorrhages [11]. Foreign studies have data on the high prognostic and diagnostic significance of IL-6 and IL-8 levels as predictors and early markers in severe bacterial infections and sepsis in premature infants [12].

To sum up, we can conclude that the state of the immune system of children from very early preterm birth, which subsequently developed severe BPD, is characterized by the activation of cellular (an increase in the number of lymphocytes and their subpopulations) and humoral immunity (an increase in the production of IL-6 and IL-8) at birth. It is characterized also in case of the disease development - a reduced ability of monocytes to present antigens, an increase in the level of IL-8 during the neonatal period, by 38-40 weeks of PCA - a decrease in the number of T-lymphocytes, T-helpers, a decrease in the effectiveness of monocyte phagocytosis, with an increased number of natural killer cells and leukocytes. In children from early preterm birth, which formed severe BPD, there is no change in the parameters of adaptive immunity throughout the entire examination period, an increase in the functional activity of $CD14^+$ $HLA\text{-}DR^+$ monocytes at birth, an increase in the synthesis of IL-8 in the neonatal period and NK- cells in 38-40 weeks of PCA.

During the formation of mild and moderate degree of BPD in all children, regardless of gestational age, significant differences similar to the above were recorded in innate immunity indicators.

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4.2. A method for predicting the development of severe bronchopulmonary dysplasia in premature infants with extremely low body weight in the neonatal period

The urgency of the problem is determined by the fact that among premature infants who survived due to the use of artificial lung ventilation (ALV), there is an increase in morbidity and mortality at an early age and infancy, which is due to both severe perinatal pathology and the formation of postresuscitation complications, one of which is bronchopulmonary dysplasia. (BLD). According to various researchers, BLD occurs in 10–25% of premature infants who got extended ALV. Bronchopulmonary dysplasia continues to be one of the main causes of mortality and morbidity in extremely low body weight (ELBW) infants. The fatal outcome in BPD is up to 36% in children during the first 3 months of life, and up to 14.5% in the first year of life. Surviving children with BLD up to 5–6 years of age are prone to more frequent occurrence of respiratory dysfunctions, the development of severe chronic pathology, in particular, obstructive pulmonary disease, which leads to high financial costs for medical and rehabilitation measures.

In children with GA of 22-27 weeks, a high incidence of severe BLD to PCA was diagnosed at 38-40 weeks. The incidence of BLD depends on birth weight, duration of ALV and is 40-45% in children with ELBW. Mortality in BLD varies from 14 to 36% during the first three months of life and then 11% during the first year of life. BLD is characterized by chronic respiratory failure (RF), long-term dependence on oxygen, recurrent broncho-obstructive syndrome, recurrent pneumonia. BLD is often transformed into obliterating bronchiolitis and bronchial asthma [66]. Establishment of the presence of clinical and radiological

signs of BLD postpones the adoption of measures aimed at preventing this pathology. Treatment of bronchopulmonary dysplasia presents serious difficulties and is accompanied by high economic costs. Therefore, the most serious consideration should be given to the early prognosis of BLD.

We have developed a method for predicting the development of severe bronchopulmonary dysplasia in children with ELBW in the neonatal period. It consists in determining the relative content of $CD14^+HLA\text{-}DR^+$ - monocytes and the absolute number of $CD4^+$ $CD25^+$ - lymphocytes in cord blood, taking into account the development of severe anemia, requiring blood transfusion and subsequent calculation of the prognostic index (PI).

The method is as follows: venous blood is taken from the umbilical cord vein into a test tube with EDTA, which is used to determine the relative content of $CD14^+$ $HLA\text{-}DR^+$ - monocytes and the absolute number of $CD4^+CD25^+$ - lymphocytes in the umbilical cord blood of children with ELBW by flow cytometry. The obtained values, taking into account the data of the child's anamnesis (the presence of a severe degree of anemia in the neonatal period, requiring blood transfusion), are used to calculate the prognostic index (PI) according to the formula developed using the discriminant analysis method:

$PI1 = 0.074 \times X1 + 6.72 \times X2 + 3.27 \times X3 - 5.31$, where

X1 - the relative content of $CD14^+HLA\text{-}DR^+$ - blood monocytes, %;

X2 - the absolute number of $CD4^+$ $CD25^+$ - lymphocytes, 10^9/l;

X3 - presence / absence of severe anemia in the neonatal period, requiring blood transfusion (1/0);

5.31- constanta.

When $PI1 < 0$, a high risk of severe bronchopulmonary dysplasia is predicted, and when $PI1 > 0$, a low risk of developing a pathological condition in premature infants with ELBW.

The sensitivity of the proposed method was calculated on the examination sample of additionally examined 47 premature infants with ELBW, is 90%, specificity - 88.9%. The efficiency of the method is 89.5%.

Example 1. A newborn boy M. (labor and delivery record No. 53117) was born to a 24-year-old primary pregnant nicotine-dependent woman. The first real pregnancy proceeded against the background of chronic placental insufficiency, subcompensated form, 1st degree of uteroplacental blood flow disturbances, acute fetal hypoxia. Premature operative labor in cephalic presentation at GA of 26 weeks. Weight and body length at birth were 990 grams, 33 cm, 6/7 points on the Apgar scale. ALV from birth for 19 days, then respiratory support using the BNCPAP method for 5 days. He was transferred to the stage of rehabilitation at the age of 27 days of life. In the neonatal period, blood transfusions were not performed. When studying serum by umbilical cord blood flow cytofluorometry, the following data were obtained: $CD14^+HLA\text{-}DR^+$ - monocytes - 21%, $CD4^+CD25^+$ - lymphocytes - 0.07×10^9/l.

The predictive index was calculated by the formula:

PI = 0.074×21 + 6.72×0.07 + 3.27×0 - 5.31 = -3.2856, which indicates a high risk of developing severe BLD.

At the age of 88 days of life in a satisfactory condition, the child was discharged with a body weight of 2536 g with a diagnosis of BLD, classical form, severe severity, stage of remission. Rd is of 0-I degree.

Example 2. Newborn boy P. (labor and delivery record No. 52391) was born to a 35-year-old bipara woman, somatically weighed down by varicose veins of the lower extremities, myopia of the 1st degree. The anamnesis has 1 artificial termination of pregnancy, 1 urgent spontaneous delivery at full-term without any peculiarities, the child is healthy. This third present pregnancy proceeded against the background of a weighed down by obstetric history (medical abortion), chronic placental insufficiency, decompensated form, disorders of uteroplacental blood flow of II-III degree, oligohydramnios, moderate preeclampsia, progressive course. Labor premature operative at 28 weeks, foot presentation. Weight and body length at birth 790 grams, 33 cm, 4/6 points on the Apgar scale. There was ALV from birth for 2 days, then respiratory support using the BNCPAP method for 2 days. He was transferred to the stage of early rehabilitation at the age of 12 days of life. Blood transfusion was not performed in the neonatal period. In the study of serum by umbilical cord blood flow cytofluorometry, the following data were obtained: $CD14^+HLA\text{-}DR^+$ - monocytes - 61%, $CD4^+CD25^+$ - lymphocytes - 0.2816×10^9/l.

The predictive index was calculated by the formula:

PI = 0.074×61 + 6.72×0.2816 + 3.27×0 - 5.31 = 1.0963, which is more than 0 and predicts a low risk of severe bronchopulmonary dysplasia.

At the age of 79 days of life in a satisfactory condition, the child was discharged home with a body weight of 2360 grams with a diagnosis of BPD, classical form, mild severity, stage of remission. RD is of 0 degree.

Example 3. A newborn girl (labor and delivery record No. 52039) was born to a 33-year-old bipara woman. The anamnesis has 1 urgent delivery and 3 medical abortions at the request of the woman. Pregnancy 5 real proceeded against the background of a burdened obstetric history (3 medical abortions), bacterial vaginosis (without debridement), genital herpes, grade I anemia, fetal growth retardation syndrome (FGRS) of I-II degree. Delivery is quick premature at 29 weeks, occipital presentation.

Weight and body length at birth were 840 grams, 32 cm, 4/6 points on the Apgar scale. There was ALV from birth for 6 days, then respiratory support using the BNCPAP method for 6 days. She was transferred to the stage of rehabilitation at the age of 25 days of life. Blood transfusion was performed in the neonatal period once. In the study of serum by umbilical cord blood flow cytofluorometry, the following data were obtained: $CD14^+HLA\text{-}DR^+$ - monocytes - 14%, $CD4^+CD25^+$ - lymphocytes - 0.13×10^9/l.

The predictive index was calculated by the formula:

PI = 0.074×14 + 6.72×0.13 + 3.27×1–5.31 = -0.1304, which is less than 0 and predicts a high risk of severe BLD.

At the age of 94 days of life in a satisfactory condition, the child was discharged with a body weight of 2000 grams with a diagnosis of BLD, classical form, severe severity, stage of remission. RD is of 0-I degree.

Example 4. Newborn girl B. (labor and delivery record No. 50427) was born to a 17-year-old primary primigravida mother with Klippel-Feil syndrome. The first real pregnancy proceeded against the background of chronic placental insufficiency, decompensated form, disorders of the uteroplacental blood flow of the III degree without centralization with the outcome in the FGRS of the I degree. Premature operative labor in breech presentation at 28 weeks.

Weight and body length at birth were 890 grams, 34 cm, 5/6 points on the Apgar scale. There was ALV from birth for 18 days, then respiratory support using the BNCPAP method for 2 days. She was transferred to the stage of rehabilitation at the age of 22 days of life. Blood transfusion was performed in the neonatal period once. In the study of serum by umbilical cord flow cytofluorometry, the following data were obtained: $CD14^+HLA\text{-}DR^+$ - monocytes - 25%, $CD4^+CD25^+$ - lymphocytes - 0.42×10^9/l.

The predictive index was calculated by the formula:

PI = 0.074×25 + 6.72×0.42 + 3.27×1–5.31 = 2.6324, which is more than 0 and predicts a low risk of severe bronchopulmonary dysplasia.

At the age of 74 days of life in a satisfactory condition, the child was discharged with a body weight of 2040 grams without a BLD diagnosis.

Thus, the proposed method makes it possible to predict severe BLD in the neonatal period, which makes it possible to correct the tactics of managing premature infants at the stages of nursing.

The inventive method for predicting the development of severe BPD in premature infants with ELBW has the following advantages in comparison with the existing ones: the method is simple to execute, includes an assessment of clinical and laboratory studies, and is minimally invasive (umbilical cord blood).

Chapter V. FUNCTIONAL STATE OF THE IMMUNE SYSTEM OF CHILDREN WITH RETINOPATHY OF PREMATURE IN THE DYNAMICS OF THE POSTNATAL PERIOD

The most common pathology in children with ELBW is retinopathy of prematurity, the cause of which is a combination of various risk factors leading to impairment of full retinal vasculogenesis. The effect of free radicals on retinal membrane structures and vessels is one of the most important mechanisms of ROP pathogenesis. BPD, necrotizing enterocolitis, IVH, RDS and cardiopathy are all "free radical diseases", namely, the excessive accumulation of free radicals affects the development of ROP.

Additional risk factors affecting the occurrence of retinopathy of prematurity are fetal hypoxia, intrauterine infections, respiratory distress syndrome, intracranial birth trauma, sepsis, anemia of prematurity. The relationship between the development of ROP and acidosis, anemia of prematurity, sepsis, and repeated blood transfusions was revealed.

According to the international classification, there are five stages of active ROP according to the localization of the process and its length:

Stage I ROP - a demarcation line appears between the vascular and avascular borders of the retina; Stage II ROP - a shaft (ridge) appears in place of the formed demarcation line; Stage III ROP - extraretinal fibrovascular proliferation (threshold ROP) is formed in the area of the shaft; Stage IV ROP - partial retinal detachment without involvement of the macular zone in the process (4a) and with retinal detachment in the macula (4c); Stage V - total retinal detachment. Therefore, it is extremely important to carefully monitor the parameters of oxygen homeostasis in children with ELBW and to provide consultations of a qualified ophthalmologist and surgical treatment if necessary (most often - laser therapy) from 4-6 weeks of life [1].

Thus, by the time of transfer to the stage of early rehabilitation, children with ELBW have a severe combined pathology - a severe ischemic or ischemic-hemorrhagic lesion of the CNS, IUI, RDS, are at a high risk for the development of BPD, syndrome of movement disorders, retinopathy of prematurity and hearing impairment, which calls for the search for and implement effective diagnostic and prognostic approaches that will help to reduce the rates of chronic pathology and disability.

The increased attention to retinopathy of prematurity is due to the high risk of developing blindness and visual disability, as a result of nursing children who were previously considered incurable. The incidence of ROP varies in different countries, reaching 24.7 per 100 thousand live births, and correlates with the degree of immaturity of the child, reaching 67% in children with ELBW [2]. The question of the participation of immune mechanisms in the development of ROP remains unstudied. In the reference, there are only a few histological works on this issue [3].

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5.1. Dynamics of changes in indicators of adaptive and innate immunity in children with ELBW who developed retinopathy of prematurity

During the study, children who subsequently developed retinopathy were divided into groups depending on gestational age and severity.

Children with retinopathy of I-III degree at GA of 22-27 weeks:

1D group - PH of III degree, n = 14;

1E group - PH of I-II degree, n = 19.

Children with retinopathy of I-III degree at GA 28-31 weeks:

2D group - PH of III degree, n = 8;

2E group - PH of I-II degree, n = 30.

The number of girls and boys in the groups was comparable and amounted to 64.3% and 35.7% in group 1, 57.9% and 42.1% in group 2, and 87,5 and 12.5% in group 3, in the 4th group 53.3% and 46.7% by gender ($p > 0.05$ in all cases). However, girls were recorded more often in the groups with retinopathy of III degree.

Children from very early preterm labor who subsequently developed retinopathy of III degree did not have significant differences in gestational age (26.0 ± 0.96 versus 26.4 ± 0.77 weeks, $p > 0.05$). However, the body weight of these children was statistically significantly lower (802.071 ± 112.4 g versus 897.3 ± 88.5 g, $p = 0.014$). In children with retinopathy of III degree, on the other hand, body weight did not differ from early preterm labor (845.0 ± 182.5 and 915.0 ± 90.2 g, $p > 0.05$), and the gestational age was significantly lower ($28,4 \pm 0.74$ versus 29.3 ± 1.3 weeks, $p = 0.017$).

According to the publication, children with less body weight and gestational age are more likely to develop severe ROP. In premature infants with GA of 22-27 weeks, threshold retinopathy of prematurity was significantly more often diagnosed, which is consistent with the authors' data on the dependence of the incidence of the disease on the maturity of the child, reaching 54-72% in children with ELBW [1, 2].

Similar results were obtained in the course of this study. Children from very early preterm labor who subsequently developed retinopathy of III degree had a lower body weight (802.071 ± 112.4 g versus 897.3 ± 88.5 g in children with ROPof stage I-II, p = 0.014), and children from early preterm birth - less gestational age (28.4 ± 0.74 versus 29.3 ± 1.3 weeks, p = 0.017). Girls from very early preterm birth were 2 times more likely to develop threshold retinopathy than boys. Other equally important causes of ROP are RDS, BLD, necrotizing enterocolitis, intraventricular hemorrhages and cardiopathies, as well as fetal hypoxia, intrauterine infections, sepsis, anemia, repeated blood transfusions.

Severe anemia in the neonatal period, regardless of gestational age, suffered from half of the children with threshold ROP. However, repeated blood transfusions were significantly more often recorded in children with GA of 22-27 weeks (3.64 ± 2.34 versus 1.74 ± 1.24 times in children with ROP of I-II degree, p = 0.01), in children with GA of 28-31 weeks did not reveal significant differences in the frequency of blood transfusions (2.12±1.46 versus 1.22±1.23 times, p> 0.05). There were no significant differences in the frequency of detection of sepsis and pneumonia depending on the severity of retinopathy. Severe bronchopulmonary dysplasia was most often observed in children with threshold retinopathy (42.9% versus 21.5% in children with HV 22-27 weeks and 37.5% versus 6.5% in children with GA of 28-31 weeks).

When studying the population and subpopulation composition of cord blood lymphocytes, the production of intracellular cytokines in children with ELBW, regardless of gestational age and stage of ROP, no significant differences were found (Table 55).

Table 55.

Population and subpopulation composition of umbilical cord blood lymphocytes of premature infants who subsequently developed retinopathy, IU (P25-P75)

Indicators	Babies from very early pre-term labor (22-27 weeks)		Babies from early pre-term birth (28-31 weeks)	
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)
Leukocytes, 10^9/l	4,7 (4,03-6,05)	5,0 (4,24-7,41)	9,55 (6,75-12,9)	6,28 (4,8-11,29)
Lymphocytes, %	68 (59-77,5)	74 (61,75-75,75)	58,5 (49,75-64)	70,5 (57,5-76,5)
Lymphocytes, 10^9/l	3,44 (2,11-3,54)	3,78 (2,63-4,55)	5,81 (4,11-7,37)	4,02 (3,11-8,26)
CD3+, %	43 (38,0-44,0)	34,5 (33,0-35)	50 (41,75-51,5)	44 (38-54)
CD3+, 10^9/l	1,27 (0,73-1,31)	1,6 (1,42-2,4)	2,59 (1,67-3,02)	1,86 (1,26-3,2)
CD19+, %	12(10-14)	9 (6-12)	14 (10,25-25,25)	14 (10-17)
CD19+, 10^9/l	0,34 (0,24-0,43)	0,41 (0,22-0,78)	1,01 (0,56-2,19)	0,68 (0,44-0,73)
CD4+, %	28 (26-31)	26,5(23,75-37,25)	33 (27,75-38,25)	32 (25-41)
CD4+, 10^9/l	0,78 (0,47-0,87)	1,31 (1,18-1,79)	1,84 (1,32-4,06)	1,35 (0,85-2,43)
CD8+, %	14 (13-15-14,75)	8,5 (5,75-13,0)	13 (11,5-18,5)	14 (10-17)
CD8+, 10^9/l	0,47 (0,20-0,53)	0,36 (0,26-0,66)	0,7 (0,62-1,7)	0,59 (0,45-0,89)
CD16+CD56+, %	2,0 (1-3)	4,0 (2,75-6,0)	9,0 (6,5-12,25)	6 (3-10)
CD16+CD56+, 10^9/l	0,04 (0,03-0,10)	0,12 (0,11-0,37)	0,36 (0,35-0,52)	0,27 (0,09-0,71)
CD4/CD8	2,3/8 (1,86-3,11)	3,55 (2,99-4,33)	2,36 (1,65-2,72)	1,85 (1,71-3,3)
CD25+CD4+, %	3 (3-6)	2 (1,25-2,0)	3 (2,5-9,0)	4 (2,75-4,25)
CD25+CD4+, 10^9/l	0,1 (0,08-0,12)	0,09 (0,06-0,24)	0,37(0,17-0,47)	0,16 (0,12-0,28)

Note. *The significance of differences between groups of children (Student's test) in all cases, p> 0.05.*

The most important place in the immune system belongs, as you know, to CD4+ lymphocytes (T-helpers), which determine and direct the nature of the immune response during infectious aggression. Upon reaching 1 month of life in children born at the time of very early preterm labor, which formed PH of III degree, there was a significant decrease in T-helpers (p1D-1E = 0.014) and B-cells (p1D-1E = 0.002) (Table 56).

Table 56.

Population and subpopulation composition of peripheral blood lymphocytes of premature babies at the age of 1 month of life, subsequently developing retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP of III degree (Group 1D, n=14)	ROP of I-II degree (Group 1E, n=19)	ROP of III degree (Group 2D, n=8)	ROP of I-II degree (Group 2E, n=30)	
Leukocytes, 10^9/l	6,3 (4,4-8,55)	7,5 (6,05-10)	10,85 (9,63-12,95)	7,55 (5,74-8,93)	**$_{2D\text{-}2E}$ =0,008**
Lymphocytes, %	59 (49-63)	60 (46-63)	54 (5071,5)	60 (56,75—74,25)	
Lymphocytes, 10^9/l	3,84 (2,14-5,8)	4,43 (3,65-6)	4,97 (3,26-5,75)	4,37 (3,44-5,67)	
CD3+, %	52,5 (49,75-53,75)	57,5 (48,75-67)	48 (44-58,5)	55 (44-62,75)	
CD3+, 10^9/l	1,80 (1,3-2,41)	2,41 (2,06-3,09)	2,38 (1,92-2,89)	2,44 (1,88-3,2)	
CD19+, %	8 (6-10)	10,5 (7,5-16,25)	18,5 (16,3-21,5)	14 (9-19)	**$_{1D\text{-}1E}$ =0,013**
CD19+, 10^9/l	0,17 (0,1-0,27)	0,51 (0,2-0,71)	0,57 (0,47-0,88)	0,60 (0,38-1,2)	**$_{1D\text{-}1E}$ =0,002**
CD4+, %	31,5 (24,5-39,25)	42,0 (39,0-52,0)	31 (24-41)	41 (31-46,5)	**$_{1D\text{-}1E}$ =0,08**
CD4+, 10^9/l	1,23 (0,79-1,65)	1,86 (1,5-2,34)	1,46 (1,1-1,7)	1,7 (1,29-2,06)	**$_{1D\text{-}1E}$ =0,014**
CD8+, %	16 (13,5-23)	18,5 (14,75-22,25)	17 (16-19,5)	15 (13-19)	
CD8+, 10^9/l	0,66 (0,4-1,07)	0,67 (0,57-1,03)	0,82 (0,69-0,92)	0,72 (0,43-0,98)	
CD16+CD56+, %	17,5 (10,25-24,75)	10,5 (9,25-14,75)	12 (8-16,5)	9 (7-14)	
CD16+CD56+, 10^9/l	0,53 (0,22-0,84)	0,45 (0,34-0,66)	0,4 (0,31-0,73)	0,39 (0,2-0,61)	
CD4/CD8	1,71 (1,08-3,05)	2,41 (1,99-3,03)	1,96 (1,69-2,16)	2,47 (1,95-3,37)	**$_{2D\text{-}2E}$ =0,04**
CD25+CD4+, %	5 (4-6)	6 (5-7)	4 (3,5-5,5)	6 (4-6)	
CD25+CD4+, 10^9/l	0,18 (0,11-0,19)	0,25 (0,18-0,42)	0,23 (0,17-0,25)	0,26 (0,18-0,31)	**$_{1D\text{-}1E}$ =0,016**

Note: *p - the level of significance of differences between groups of children (Mann-Whitney criterion): group 1D - children with GA of 22-27 weeks, who formed ROP of severe III degree, group 1E - children with ROP at 22-27 weeks, who developed ROP of I-II degree; Group 2D - children with GA of 28-31 weeks, who developed ROP of severe severe III degree, 2E group - children with GA of 28-31 weeks, who developed ROP of I-II degree.*

A decrease in the absolute number of activated cells with the $CD25^+CD4^+$ receptor was also found in this group of newborns ($p_{1D-1E} = 0.016$).

By 38-40 weeks of PCA, a reduced number of CD4 cells ($p_{1D-1E} = 0.05$) and B-lymphocytes ($p_{1D-1E} = 0.017$) in the peripheral blood of children of group 1 persists against the background of an increase in NK cells ($p_{1D-1E} = 0.01$) (Table 57).

Table 57.

Population and subpopulation composition of peripheral blood lymphocytes of premature infants with ELBW at 38-40 weeks of PCA, which formed retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm labor (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
Leukocytes, 10^9/l	6,2 (4,98-6,74)	6,45 (5,99-7,91)	7,5 (6,98,7)	6,33 (5,36-7,6)	
Lymphocytes, %	74 (67,5-81,5)	64,5 (60,25-69,25)	68 (63,5-69)	65,5 (60,75-75,75)	
Lymphocytes, 10^9/l	4,14 (3,63-4,62)	4,8 (3,59-5,09)	4,59 (4,39-6,19)	4,65(4-5,06)	
CD3+, %	50,5 (40,5-56)	56 (50-59)	47 (42,5-51)	50 (45-52,75)	
CD3+, 10^9/l	1,78 (1,6-2,37)	2,36 (2,03-2,73)	2,13 (1,94-2,49)	2,22 (1,99-2,55)	
CD19+, %	24 (16,25-32)	28 (19-30)	37 (31,5-42,5)	26 (19,5-29)	2D-2E **=0,017**
CD19+, 10^9/l	1,21 (0,63-1,3)	0,68 (0,58-1,53)	1,8 (1,43-2,44)	1,12 (0,84-1,33)	1D-1E **=0,002** 2D-2E **=0,04**
CD4+, %	27,5 (23,5-34,25)	39 (33-44)	29 (28-35,5)	34,5 (29,5-38,5)	1D-1E **=0,05**

CD4+, 10^9/l	1,07 (0,97-1,48)	1,71 (1,23-1,85)	1,36 (1,26-1,63)	1,56 (1,28-1,83)	1D-1E **=0,07**
CD8+, %	20,5 (12,75-26,25)	15 (15-19)	15 (13-18)	14,5 (12-19)	
CD8+, 10^9/l	0,72 (0,5-1,07)	0,62 (0,49-0,76)	0,87 (0,6-0,98)	0,64 (0,57-0,8)	
CD16+CD56+, %	20 (13-23,5)	9 (6-15)	10 (5,5-17,5)	13,5 (10,5-16,5)	
CD16+CD56+, 10^9/l	0,78 (0,51-1)	0,3 (0,29-0,59)	0,66 (0,26-0,95)	0,63 (0,4-0,77)	1D-1E **=0,010**
CD4/CD8	1,65 (1,26-1,94)	2,6 (2,11-2,8)	2,1 (1,36-2,64)	2,17 (1,78-3,17)	
CD25+CD4+, %	4 (3,75-5)	5 (4-6)	5 (4-5)	5 (4-6)	1D-1E **=0,03**
CD25+CD4+, 10^9/l	0,16 (0,14-0,18)	0,21 (0,18-0,25)	0,22 (0,2-0,23)	0,24 (0,19-0,28)	1D-1E **=0,010**

Note: *p - the significance of differences between groups of children (Mann-Whitney criterion): groups 1 and 3 - children who developed ROP of III degree, groups 2 and 4 - children who developed ROP of I and II degree.*

The number of CD25+CD14+, both in absolute and relative numbers, remains at the same reduced level ($p_{1D\text{-}1E} = 0.01$, $p_{1D\text{-}1E} = 0.03$).

On the other hand, for children born at the time of early preterm labor who have developed PH of III degree, an increase in the number of B-cell immunity is characteristic ($p_{1D\text{-}1E} = 0.017$).

The concentration of cytokines in serum or other biological fluids shows the current state of the immune system. However, the determination of the level of cytokine production by blood mononuclear cells reflects the functional state of cells (spontaneous production) or their potential ability to respond to an antigenic stimulus (induced production), then the method of intracellular staining of cytokines makes it possible, using flow cytometry, to determine the population belonging of cells that produce a particular cytokine [3].

The production of umbilical cord blood intracellular cytokines in all premature infants did not differ statistically significantly (Table 58).

Table 58.

Levels of intracellular cytokines in the umbilical cord blood of premature infants with retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)	
	ROP III (Group 1D, n=14)	**ROP I-II (Group 1E, n=19)**	**ROP III (Group 2D, n=8)**	**ROP I-II (Group 2E, n=30)**
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	2,85 (1,36-3,95)	3,0 (1,76-5,82)	1,89 (1,71-4,64)	2,36 (1,66-5,82)
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	4,58 (3-4,58)	4,92 (2,94-8,8)	4,58 (1,52-6,13)	3,47 (1,64-7,67)
$CD4^+IL\text{-}4^+$ self-existing, %	1,99 (0,9-2,93)	1,74 (0,88-3,16)	0,83 (0,73-2,0)	2,08 (0,83-3,17)
$CD4^+IL\text{-}4^+$ suscitate, %	4,59 (2,43-5,49)	4,05 (2,89-5,01)	3,6 (3,22-4,91)	3,8 (2,97-5,78)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,6 (1,36-1,77)	1,38 (21,21-1,74)	1,49 (1,39-1,84)	1,79 (1,43-2,13)
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,041 (0,98-1,26)	1,25 (1,08-1,46)	1,19 (1,11-1,2)	1,18 (0,65-1,36)

Note. *The significance of differences between groups of children (Student's test) in all cases, p> 0.05.*

When analyzing the indices of intracellular cytokines of peripheral blood in premature infants of the 3rd group, there was a decrease in the content of T-helpers spontaneously synthesizing IFN-γ (p_{2D-2E} = 0.04) (Table 59).

In children from very early preterm birth, no significant differences in the production of intracellular cytokines were found.

Table 59.

Levels of intracellular cytokines in the peripheral blood of premature infants at the age of 1 month of life, subsequently developing retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	1,54 (1,04-3,2)	2,95 (1,24-4,61)	2,52 (1,47-2,83)	2,31 (1,29-6,38)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	3,05 (2,27-5,87)	3,53 (2,61-5,35)	5,17 (3,17-5,24)	5,33 (2,48-7,27)	$_{2D\text{-}2E=}$**0,04**
$CD4^+IL\text{-}4^+$ self-existing, %	1,17 (0,75-2,51)	1,66(1,02-2,51)	1,62 (0,94-1,96)	1,21 (1,03-2,84)	
$CD4^+IL\text{-}4^+$ suscitate, %	1,89 (1,6-3,28)	2,87 (1,71-4,75)	4,04 (2,15-4,25)	3,67 (2,31-4,84)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,36 (1,22-1,55)	1,3(1,18-1,55)	1,53(1,37-1,62)	1,82 (1,32-2,17)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	1,73 (1,46-1,89)	1,64 (1,51-1,95)	2,41 (1,62-2,82)	1,29 (1,12-1,41)	

Note: *p - the significance of differences between groups of children (Mann-Whitney test): group 1D - children with Ga of 22-27 weeks, who developed ROP of severe degree III, 1E group - children with ROP at 22-27 weeks, who developed ROP of degrees I-II; Group 2D - children with GA of 28-31 weeks, who developed ROP of severe degree III, 2E group - children with GA of28-31 weeks, who developed ROP of I-II stages.*

In children born at 28-31 weeks of gestation and formed degree III of PH, there was an increase in CD11b+CD14+, monocytes ($p_{2D\text{-}2E}$ = 0.045), which indicates the predominance of mature cells in the population and an increased readiness of effector cells to participate in processes of antigenic presentation and intercellular interaction (Table 60).

The increase in CD14+HLA-DR+ monocytes of umbilical cord blood in children with Ga of 28-31 weeks with threshold retinopathy ($p_{2D\text{-}2E}$ = 0.01) may be associated with a higher frequency of infectious diseases (pneumonia) in relation to children with I-II degree of ROP (37.5% versus 26.7%).

Table 60.

Markers of activation of umbilical cord blood monocytes of premature infants who subsequently developed retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
CD11b+CD14+, %	31,0 (15,0-60,0)	50(11,0-68)	56 (46,7-61,5)	35(21,5-48,5)	p_{2D-2E} **=0,045**
CD11b+CD14+, abs.	0,09 (0,03-0,09)	0,14 (0,09-0,19)	0,33 (0,19-0,39)	0,19 (0,11-0,23)	
CD64+CD14+, %	8,0 (7,5-16,75)	42,0 (20,0-44,0)	20 (15-32)	42 (38-44)	p_{1D-1E} **=0,0001** p_{2D-2E} **=0,07**
CD64+CD14+, 10^9/l	0,05 (0,05-0,10)	0,19 (0,11-0,24)	0,10 (0,07-0,21)	0,19 (0,12-0,24)	p_{1D-1E} **=0,01**
CD14+HLA-DR+, %	39,0 (15,0-58,0)	25,0 (15,75-42,75)	56,5 (43,75-63,3)	28 (18,5-46,75)	p_{2D-2E} **=0,010**
CD14+HLA-DR+, 10^9/l	0,09 (0,08-0,12)	0,12 (0,08-0,17)	0,26 (0,19-0,35)	0,11 (0,06-0,17)	
CD71+CD14+, %	11,0 (10,5-12,5)	13,0 (7,75-19,75)	24 (12-24)	15 (12-22)	
CD71+CD14+, 10^9/l	0,12 (0,12-0,14)	0,18 (0,11-0,25)	0,11 (0,08-0,30)	0,20 (0,14-0,28)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 1D - children with GA of 22-27 weeks, who developed ROP of severe degree III, 1E group - children with ROP at 22-27 weeks, who developed ROP of stages I-II; Group 2D - children with GA of 28-31 weeks, who developed ROP of severe degree III, 2E group - children with GA of 28-31 weeks, who developed ROP of I-II degrees.*

In children born at 22-27 weeks, who developed ROP of degree III, there was a significant decrease in both absolute and relative values of CD64+CD14+, (p_{1D-1E} = 0.01, p_{1D-1E} = 0.0001), which are capable of bind immune complexes and facilitate phagocytosis of pathogens. The incidence of pneumonia in group 1D is 78.57% versus 63.16% in group 1E, sepsis is 36.6% versus 21% of cases, respectively.

The level of anti-inflammatory cytokine IL-6 in newborns of the 1D group ($p_{1D-1E} = 0.014$) and IFN-γ of the 2D group ($p_{2D-2E} = 0.004$) was significantly lower than in children with PH of I-II degree, which may indicate a violation of the protective properties of the immune system (Table 61).

Table 61.

Levels of umbilical cord blood cytokines in premature infants who subsequently developed retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
IFN- γ, pg/ml	13,32 (12,36-14,27)	11,26 (10,46-12,29)	0 (0,0-1,95)	10,33 (6,35-11,76)	$_{=}^{2D-2E}$ **0,004**
IL-6, pg/ml	20,75 (17,32-105,9)	139,36 (101,5-155,5)	6,04 (3,37-15,0)	9,84 (4,07-19,85)	1D-1E $_{=}$0,014
IL-8, pg/ml	118,85 (90,05-162,1)	69,31 (55,85-142,2)	28,28 (15,73-40,29)	25,9 (16,83-41,95)	
IL-4, pg/ml	0,61 (0,51-0,81)	0,35 (0,22-0,90)	0,93 (0,5-1,08)	0,61 (0,49-0,97)	

Note: *p- significance of differences between groups of children (Mann-Whitney criterion): group 1D - children with GA of 22-27 weeks, who developed ROP of severe of III degree, 1E group - children with ROP at 22-27 weeks, who developed ROP of I-II degrees; Group 2D - children with GA of 28-31 weeks, who developed ROP of severe of III degree, 2E group - children with GA of 28-31 weeks, who developed ROP of I-II stages.*

At the age of 1 month of life, a significant decrease in the absolute and relative number of CD64+/CD14+ cells ($p_{1D-1E} = 0.01$) was noted in premature babies of the 1st group (Table 62).

Table 62.

Markers of activation of peripheral blood monocytes in premature infants at the age of 1 month of life, subsequently developing retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
CD11b+CD14+, %	51 (42-55,5)	68 (49-82)	56 (53,3-57,8)	70,5 (64,5-81,25)	
CD11b+CD14+, abs.	0,43 (0,38-0,47)	0,5 (0,29-0,75)	0,54 (0,37-0,89)	0,49 (0,36-0,61)	
CD64+CD14+, %	27,0 (20,25-37,8)	56,5 (34,0-73,0)	11,0 (8,5-18,0)	30 (14,25-55,75)	$_{1D-1E=}$**0,01** $_{2D-2E}$ **=0,025**
CD64+CD14+, 10^9/l	0,25 (0,13-0,30)	0,35 (0,22-0,65)	0,13 (0,07-0,18)	0,22 (0,06-0,37)	$_{1D-1E=}$**0,01**
CD14+HLA-DR+, %	70 (67,5-73,25)	66,5 (48,5-83,3)	62 (56,8-67,3)	67,5 (59,25-75)	$_{2D-2E}$ **=0,09**
CD14+HLA-DR+, 10^9/l	0,43 (0,38-0,49)	0,54 (0,29-0,88)	0,61 (0,47-0,91)	0,51 (0,33-0,58)	$_{2D-2E}$ **=0,025**
CD71+CD14+, %	10 (3,75-15,5)	14 (9,75-17)	27 (20,5-30)	12,5 (6-20,75)	
CD71+CD14+, 10^9/l	0,08 (0,07-0,11)	0,09 (0,065-0,16)	0,22 (0,13-0,38)	0,08 (0,04-0,13)	$_{2D-2E}$ **=0,08**

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): group 1D - children with GA of 22-27 weeks, who developed ROP of severe of III degree, 1E group - children with ROP at 22-27 weeks, who developed ROP of I-II degrees; Group 2D - children with GA of 28-31 weeks, who developed ROP of severe III degree, 2E group - children with GA 28-31 of weeks, who developed ROP of I-II stages.*

An increase in the number of CD14 / HLA-DR ($p_{1D-1E} = 0.025$) was typical for children of the 2nd group with ROP of stage III.

When assessing serum cytokines in the peripheral blood of children of all groups, no statistically significant differences were found (Table 63).

Table 63.

Cytokine levels in children at the age of 1 month of life who subsequently developed retinopathy, IU (P25-P75)

Indicators	Babies at GA of 22-27 weeks		Babies at GA of 28-31 weeks	
	ROP III (Group 1D, n=14)	**ROP I-II (Group 1E, n=19)**	**ROP III (Group 2D, n=8)**	**ROP I-II (Group 2E, n=30)**
IFN- γ, pg/ml	4,25 (3,87-9,51)	1,1 (0,0-6,66)	2,05 (1,63-2,19)	1,86 (1,39-1,91)
IL-6, pg/ml	7,55 (4,1—16,62)	6,12 (4,69-13)	22 (7,21-38,09)	5,53 (4,07-10,48)
IL-8, pg/ml	30,63 (25,33-41,42)	27,9 (26,24-32,47)	24,58 (19,56-38,13)	14,73 (12,67-24,04)
IL-4, pg/ml	1,8 (1,74-1,84)	1,36 (0,89-1,38)	2,05 (1,63-2,19)	1,86 (1,39-1,9)

Note. *The significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

Analysis of intracellular cytokines showed that upon reaching 38-40 weeks of PCA, a significantly increased number of $CD4^+IL\text{-}4^+$ cells in the stimulated test was observed in children of the 2D group ($p_{2D\text{-}2E} = 0.036$) (Table 64).

Table 64.

Levels of peripheral blood intracellular cytokines in children at 38-40 weeks of PCA who formed retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	**ROP I-II (Group 1E, n=19)**	**ROP III (Group 2D, n=8)**	**ROP I-II (Group 2E, n=30)**	
$CD4^+CD3^+IFN\text{-}\gamma^+$ self-existing, %	1,93 (1,27-4,07)	3,23 (2,28-5,18)	3,68 (1,88-3,87)	2,81 (2,26-5,89)	
$CD4^+IFN\text{-}\gamma^+$ suscitate, %	4,82 (2,06-6,3)	6,87 (4,95-8,87)	4,51 (2,4-5,08)	3,83 (2,63-6,41)	
$CD4^+IL\text{-}4^+$ self-existing, %	1,25 (0,91-4,32)	1,32 (1,29-3,54)	2,1 (0,97-2,39)	1,34 (1,03-2,01)	
$CD4^+IL\text{-}4^+$ suscitate, %	2,22 (2,06-4,39)	3,7 (2,22-6,2)	4,35 (2,76-5,02)	3,77 (3,2-4,38)	$_{2D\text{-}2E}$ =0,036
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ self-existing, c.u.	1,4 (1,22-1,48)	1,37 (1,27-1,82)	1,72 (1,64-1,83)	1,79 (1,49-2,11)	
$CD4^+IFN\text{-}\gamma^+$ / $CD4^+IL\text{-}4^+$ suscitate, c.u.	2,15 (1,32-2,75)	1,73 (1,4—2,31)	0,96 (0,86-1,04)	1,06 (0,98-2,52)	2D-2E =0,005

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): groups 1 and 3 - children who have developed ROP of stage III, groups 2 and 4 - children who have developed ROP of stage I and II.*

Among the markers of monocyte activation, there was an increase in the number of CD14+HLA-DR in children of the 1D group ($p_{1D-1E} = 0.017$) and a decrease in the absolute number of $CD14^+$ $CD64^+$ monocytes ($p_{1D-1E} = 0.01$); in children of the 2D group, a decrease in the proportion of CD11b+ was recorded. CD14+, -cells ($p_{2D-2E} = 0.004$) (Table 65).

Table 65.

Activation markers of peripheral blood monocytes in children at 38-40 weeks of PCA, who formed retinopathy, IU (P25-P75)

Indicators	Babies from very early preterm labor (22-27 weeks)		Babies from early preterm birth (28-31 weeks)		P
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)	
CD11b+CD14+, %	77,0 (75,0-77,25)	72 (68-76)	71,5 (68,3-74,5)	82 (78,3-86,5)	**$_{2D-2E}$ 0,004**
CD11b+CD14+, abs.	0,24 (0,22-0,26)	0,39 (0,25-0,78)	0,52 (0,41-0,53)	0,54 (0,39-0,62)	
CD64+CD14+, %	22 (17,5-32,5)	29 (22,0-56,5)	49 (44,3-56,25)	73 (65-87)	**$_{2D-2E}$ 0,09**
CD64+CD14+, 10^9/l	0,10 (0,09-0,12)	0,35 (0,25-063)	0,33 (0,24-0,44)	0,5 (0,42-0,6)	**$_{1D-1E}$ 0,01**
CD14+HLA-DR+, %	81 (77-83,25)	67 (57,3-69,8)	74 (65,5-85)	75,5 (63,25-79)	**$_{1D-1E}$ 0,01**
CD14+HLA-DR+, 10^9/l	0,32 (0,28-0,55)	0,35 (0,27-0,5)	0,66 (0,52-0,73)	0,5 (0,42-0,59)	
CD71+CD14+, %	11,5 (9,75-16,5)	15 (13-23)	17 (9,5-19,5)	15,5 (10,5-24)	
CD71+CD14+, 10^9/l	0,07 (0,03-0,09)	0,09 (0,08-0,14)	0,08 (0,06-0,14)	0,1 (0,06-0,15)	

Note: *p - significance of differences between groups of children (Mann-Whitney criterion): groups 1 and 3 - children who developed ROP of stage III, groups 2 and 4 - children who developed ROP stage I and II.*

There were no significant differences in the comparative analysis of the cytokine status of all premature infants (Table 66).

Table 66.

Levels of peripheral blood cytokines in children at 38-40 weeks of PCA who have developed retinopathy, IU (P25-P75)

Indicators	Babies at GA of 22-27 weeks		Babies at GA of 28-31 weeks	
	ROP III (Group 1D, n=14)	ROP I-II (Group 1E, n=19)	ROP III (Group 2D, n=8)	ROP I-II (Group 2E, n=30)
IFN- γ, pg/ml	1,93 (1,1-3,6)	0 (0-5,2)	2,15 (0,556,69)	3,6 (0-5,7)
IL-6, pg/ml	3,97 (3,77-4,8)	3,78 (2,46-4,35)	4,58 (3,33-11,32)	5,68 (2,89-12,24)
IL-8, pg/ml	22,13 (14,99-29,28)	14,71 (12,18-19,89)	11,87 (11,71-12,88)	13,04 (12,22-34,06)
IL-4, pg/ml	2,47 (2,12-2,76)	2,05(1,89-4,77)	1,97 (1,68-2,19)	2,22 (2,01-2,46)

Note. *Significance of differences between groups of children (Mann-Whitney test) in all cases, p> 0.05.*

According to the results of the immunological study, significant differences in children with threshold retinopathy were revealed in indicators of innate immunity of umbilical cord blood: a decrease in adhesion molecules on monocytes, statistically significant in children at GA of 22-27 weeks and at the tendency level in children at GA of 28-31 weeks. An increase in the percentage of activated $CD14^{+}HLA\text{-}DR$ monocytes in newborns from early preterm labor and the absence of such differences in infants at GA of 22-27 weeks, a decrease in IL-6 production in deeply premature infants and IFN-γ in premature at GA of 28-31 weeks.

By the end of the neonatal period, the ROP development of stage III in children from very early preterm labor was accompanied by a decrease in the number of B-lymphocytes, immunoregulatory index (CD4/CD8), CD4+ lymphocytes, and regulatory $CD4^{+}CD25^{+}$cells. The results of a study on a decrease in the populations of lymphocytes and regulatory cells in premature infants are consistent with the publication data, indicating these changes with an increase in the severity of retinopathy [4]. By the end of the disease at 38-40 weeks of PCA, the revealed decrease in T-helpers and activated subpopulations persisted, an increase in the absolute number of natural killer cells and $CD14^{+}HLA\text{-}DR^{+}$ -monocytes was observed. In children from early preterm birth, which subsequently developed retinopathy of stage III at 1 month of life, there is an increase in leukocytes and a decrease in intracellular production of IFN-γ upon stimulation of CD4 + cells, the number of activated $CD14^{+}HLA\text{-}DR^{+}$ - and CD14+CD71+ - monocytes increases. Upon reaching 38-40 weeks of PCA in the indicators of adaptive immu-

nity, an increase in the proportion of B-lymphocytes, intracellular production of IL-4 and a decrease in the adhesive ability of monocytes are recorded. Congenital immunity is characterized by a decrease at the level of a trend in the percentage of $CD14^{+}CD64^{+}$ monocytes and a significant decrease in the relative number of $CD14^{+}CD11b^{+}$ cells.

The differences that we identified in the parameters of the immune system in premature infants with retinopathy in the active phase of the disease are apparently due to the degree of bronchopulmonary dysplasia transferred in the postnatal period: severe BPD, which was recorded 2.0 and 5.7 times more often with threshold retinopathy in children from very early and early preterm birth.

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5.2. A method for predicting the development of the threshold stage of retinopathy in premature infants with extremely low body weight

The most difficult task is to predict the development and nature of the course of the disease, given that the pathogenesis of ROP is not fully understood, despite many years of research.

The principles of ROP screening currently accepted in Russia include examination of the fundus with a wide pupil by indirect ophthalmoscopy of all premature babies born before 35 weeks of gestation or weighing less than 2000 g (international criteria are gestational age at birth up to 32 weeks and weight less than 1500 g) with the first examination, as a rule, at the age of 4-6 weeks of life and subsequent periodic examinations carried out repeatedly until the process of retinal vascularization is completely completed or until the development of the so-called threshold stage of ROP, requiring therapeutic intervention. The threshold

is considered to be the III stage of the active phase of the disease with the spread of the extraretinal process to 5 consecutive or 8 total hour meridians. The cost of existing methods for predicting the course of retinopathy of prematurity (ROP) makes it relevant to search for new simple and informative signs of disease progression.

We have developed a method for predicting the development of the threshold stage of retinopathy in premature infants with extremely low body weight based on clinical and laboratory data using the method of mathematical modeling. The technical result when using the invention is to increase the efficiency of forming a risk group for the development of a threshold ROP.

The method is carried out as follows: assess the sex of the child and body weight at birth, the level of hemoglobin in peripheral blood on the hematology analyzer "ABX Micros 60-OT18" (France) on the 1st day of life and the duration of the child's stay in the intensive care unit (ICU).

A survey of 55 deeply premature infants with ELBW was carried out. It was divided into 2 groups (using the copy-pairs method):

Group 1: children who did not have ROP of stage III (n = 23);

Group 2: children with diagnosed ROP of stage III (n = 22).

When forming the groups, the comparability of children for the main, competing and concomitant diseases was taken into account. Ophthalmological examination was carried out in children, starting from 4 weeks of life, regularly, every 1-2 weeks until the process of retinal vascularization is complete or until the threshold stage of ROP, requiring therapeutic intervention.

As a result of our studies, we identified predictors of a high risk of stage III retinopathy in newborns with extremely low body weight. Using the method of discriminant analysis, a mathematical model for predicting this pathology has been developed, which consists in determining the prognostic index (PI1) according to the formula:

$PI = 1.804 \times X1 - 0.0095 \times X2 - 0.0285 \times X3 + 0.0963 \times X4 + 9.563$, where

X1 - gender of the child (female/male) (1/0);

X2 is body weight at birth, g;

X3 - peripheral blood hemoglobin content on the 1st day of life, g/l;

X4 is the number of days spent in the NICU;

9,563 - Const

If PI is more than 0, a high risk of stage III retinopathy is predicted, and if PI is less than 0, a low risk of disease progression is predicted.

The specificity of our proposed method is 80.6%, the sensitivity is 87.2%. The efficiency of the method is 83.9%.

Example 1. A premature girl (labor and delivery record No. 3039), was born to a 23-year-old bipara woman, somatically weight down by hypertensive neurocirculatory dystonia. The anamnesis 1 has urgent labor. The second present pregnancy proceeded against the background of chronic fetal-placental insufficiency,

decompensated form, III degree uteroplacental blood flow disorders without centralization of blood circulation, severe preeclampsia. There was premature operative delivery in a transverse position at GA of 28 weeks. Weight and body length at birth were 820 grams, 34 cm, 4/6 points on the Apgar scale. There was ALV from birth for 9 days, followed by respiratory support using the BNCPAP method for 9 days. She was transferred to the stage of rehabilitation at the age of 23 days of life. Indicators of red blood at birth were: hemoglobin 151 g/l, hematocrit 43.8%, erythrocytes 3.78×101^2/l.

The predictive index was calculated by the formula:

PI = 1.804 × 1 - 0.0095 × 820 - 0.0285 × 151 + 0.0963 × 23 + 9.563 = 1.477, which is more than 0 and predicts a high risk of threshold retinopathy formation.

At the age of 35 days of life, a routine ophthalmological examination was diagnosed with ROP of stage II, by 42 days of life - ROP of stage III in both eyes, which required surgical treatment. At the age of 82 days of life in a satisfactory condition, the child was discharged with a body weight of 2152 g.

Example 2. A premature boy (labor and delivery record No. 649), was born to a 37-year-old primigravida woman. Pregnancy proceeded against the background of a weight down by obstetric history (primary infertility, in vitro fertilization, 4 attempts), chronic feto-placental insufficiency, decompensated form, impaired uteroplacental blood flow of the III degree, gestational diabetes mellitus, severe preeclampsia HELLP syndrome (cardiac form). There was delivery premature operative at 26 - 27 weeks, cephalic presentation. Weight and body length at birth were 690 grams, 28 cm, 4/6 points on the Apgar scale. There was from birth for 25 days, then respiratory support using the BNCPAP method for 15 days. He was transferred to the stage of rehabilitation at the age of 42 days of life. The indices of red blood at birth were: hemoglobin 146 g/l, hematocrit 42.6%, erythrocytes 3.58×101^2/l.

The predictive index was calculated by the formula:

PI = 1.804 × 0 - 0.0095 × 690– 0.0285 × 146 + 0.0963 × 42 + 9.563 = 2.8916, which is more than 0 and predicts a high risk of threshold retinopathy formation.

At the age of 42 days of life, during a routine ophthalmological examination, ROP of stage II was diagnosed, by day 92 - ROP of stage III in both eyes, which required surgical intervention. At the age of 108 days of life in a satisfactory condition, the child was discharged with a body weight of 2300 g.

Example 3. A premature girl (labor and delivery record No. 434) was born to a 34-year-old bipara woman, weight down by B-20 of stage III. The anamnesis 1 has urgent delivery and 3 medical abortions at the request of the woman. Pregnancy 5 real proceeded against the background of a weight down by obstetric history (3 medical abortions), bacterial vaginosis (without debridement), genital herpes, grade I anemia. Delivery is quick premature at 29 weeks, occipital presentation. Birth weight and length were 840 grams, 32 cm, 5/6 points on the Apgar scale. There was ALV from birth for 6 days, then respiratory support using the BNCPAP

method for 4 days. He was transferred to the stage of rehabilitation at the age of 14 days of life. The indices of red blood at birth were: hemoglobin 160 g/l, hematocrit 46.7%, erythrocytes 3.71×10^{12}/l.

The predictive index was calculated by the formula:

PI = 1.804×1 - 0.0095×990– 0.0285×160 + 0.0963×14 + 9.563 = -1.2498, which is less than 0 and predicts a low risk of threshold retinopathy development.

At the age of 30 days of life, during a routine ophthalmological examination, ROP of stage I was diagnosed, by the age of 65 - stage II ROP in both eyes without further progression. At the age of 73 days in a satisfactory state of life, the child was discharged with a body weight of 2256 g.

Example 4. A premature boy (labor and delivery record No. 107), was born to a 41-year-old bipara woman, somatically weight down by a paranoid form of schizophrenia. The anamnesis 1 has artificial termination of pregnancy. This pregnancy, the second present, proceeded against the background of a weight down by obstetric history (medical abortion), chronic fetal-placental insufficiency, decompensated form, III degree uteroplacental blood flow disturbances without centralization of blood circulation, severe preeclampsia, bilateral hydrothorax, hydropericardium. There were delivery premature operative at 25 - 26 weeks, foot presentation. Weight and body length at birth - 770 grams, 30 cm, 5/5 points on the Apgar scale. Mechanical ventilation from birth for 7 days of life, then respiratory support using the BNCPAP method for 10 days. He was transferred to the stage of early rehabilitation at the age of 19 days of life. Indicators of red blood at birth: hemoglobin 168 g/l, hematocrit 49.5%, erythrocytes 4.31 × 1012/l.

The predictive index was calculated by the formula:

PI = 1.804 × 0 - 0.0095 × 770 - 0.0285 × 168 + 0.0963 × 19 + 9.563 = - 0.71, which is less than 0 and predicts a low risk of threshold retinopathy development.

At the age of 35 days of life with a planned ophthalmological examination,ROP of stage I was diagnosed, at the age of 42 days - ROP of stage II without subsequent progression. At the age of 75 days of life in a satisfactory condition, the child was discharged with a body weight of 2356 g.

Thus, predicting the development of threshold retinopathy of prematurity by the proposed method allows to reduce the number of severe stages of ROP due to early detection of children prone to the development of the disease.

The inventive method for predicting the formation of the threshold stage of retinopathy in deeply premature infants with EBMT has the following advantages in comparison with the existing ones: the method is simple to execute, includes the assessment of clinical and laboratory studies, which are carried out in accordance with the standard in any medical institution, does not require expensive equipment.

5.3. A method for predicting the formation of the threshold stage of retinopathy of prematurity in children with extremely low body weight in the early neonatal period

We have developed a method for predicting the development of the threshold stage of retinopathy in premature infants with extremely low body weight in the early neonatal period based on the immunological parameters of umbilical cord blood using the method of mathematical modeling. The technical result when using the invention is the identification of a risk group for the implementation of threshold retinopathy in premature infants with ELBW.

The method is carried out as follows: the collection of venous blood from the umbilical cord vein is carried out in two test tubes: the first test tube is used to determine the relative content of CD14+CD64+ - monocytes in blood plasma by flow cytofluorometry; the second - to determine the concentration of IL-4 and IL-6 by enzyme-linked immunosorbent assay in the blood serum of children with ELBW.

To achieve this goal, 71 children with ELBW at GA of 22-31 weeks were examined, who formed ROP at 38-40 weeks of PCA, which were subdivided into groups depending on the stage of the disease:

Group 1 - children with diagnosed with ROP of stage III (n = 22);

Group 2 - children with diagnosed with ROP of stage I-II (n = 49).

When forming the groups, the comparability of children for the main, competing and concomitant diseases was taken into account. Ophthalmologic examination was carried out in children, starting from the 4th week of life, regularly, every 1-2 weeks until the process of retinal vascularization is complete or until the threshold stage of ROP, requiring therapeutic intervention.

As a result of the studies, the most informative indicators of a high risk of realization of retinopathy of prematurity of stage III in children with ELBW were revealed. Using the method of discriminant analysis, a mathematical model for predicting this pathology has been developed, which consists in determining the prognostic index (PI1) according to the formula:

$PI = -0{,}138 \times X_1 - 0{,}015 \times X_2 - 3{,}41 \times X_3 + 6{,}19$, where

X_1 – CD14+CD64+ monocytes, %;

X_2 – IL-6 content, pg/ml;

X_3 – IL-4 content, pg/ml;

6,19 – Const

If PI is more than 0, a high risk of realization of threshold retinopathy of prematurity is predicted, and if PI is less than 0, a conclusion is made about a low risk of progression of this pathology.

The sensitivity of the proposed method is 86.4%, the specificity is 91.9%. The efficiency of the method is 89.15%.

Example 1. Premature girl G. (labor and delivery record No. 2516) was born in a 39-year-old bipara woman, somatically weight down by arterial hypertension of II degree, hypothyroidism. The anamnesis has antenatal fetal death. The second real pregnancy proceeded against the background of chronic placental insufficiency, subcompensated form, III degree disorders of uteroplacental blood flow without centralization of blood circulation, fetal growth retardation syndrome (FGRS). There were premature operative labor at 26 weeks. Birth weight and length were 820 grams, 31 cm, 6/7 points on the Apgar scale. Respiratory support using the BNCPAP method for 7 days, no ALV was performed. She was transferred to the stage of rehabilitation at the age of 15 days of life. Cord blood parameters at birth: CD14 + CD64 + monocytes - 8%, IL-6 - 20.75 pg/ml, IL-4 - 0.22 pg/ml.

The predictive index was calculated by the formula:

PI = -0.138 × 8 - 0.015 × 20.75 - 3.41 × 0.22 + 6.19 = 4.02, which is more than 0 and predicts a high risk of threshold retinopathy development.

At the age of 43 days of life, a routine ophthalmological examination was diagnosed with ROP of stage II, by 56 days of life - ROP of stage III in both eyes, which required surgical treatment. At the age of 89 days of life in a satisfactory condition, the child was discharged with a body weight of 2065 g.

Example 2. Premature girl Sh. (labor and delivery record No. 1893) was born in a 30-year-old primigravida pregnant woman, somatically weight down by obesity, arterial hypertension of the 1st degree, varicose veins. The anamnesis has infertility, uterine fibroids. Pregnancy proceeded against the background of gestational diabetes mellitus, chronic fetal hypoxia, threat of termination, chronic placental insufficiency, decompensated form, III degree of uteroplacental blood flow disturbance, FGRS. Labor premature operative at GA of 30 weeks.

Weight and body length at birth were 520 grams, 26 cm, 4/5 points on the Apgar scale. There was ALV from birth for 1 day, then respiratory support using the BNCPAP method - 1 day. Cord blood parameters at birth: CD14 + CD64 + monocytes - 13%, IL-6 - 15.13 pg/ml, IL-4 - 0.93 pg/ml.

The predictive index was calculated by the formula:

PI = -0.138×13 - 0.015×15.13 - 3.41×0.93 + 6.19 = 0.99, which is more than 0 and predicts a high risk of developing threshold retinopathy.

She was transferred to the stage of rehabilitation at the age of 8 days of life. At the age of 48 days of life, during a routine ophthalmological examination, ROP of stage II was diagnosed, by the 75th day of life - ROP of stage III in both eyes, which required surgical intervention. At the age of 123 days of life in a satisfactory condition, the child was discharged with a body weight of 2005 g.

Example 3. Premature boy N. (labor and delivery record No. 537) was born to a 27-year-old multigravida woman, somatically not weight down. The anamnesis has urgent labor andone medical abortion at the request of the woman. Pregnancy proceeded against the background of the threat of termination, preeclampsia of moderate severity, chronic placental insufficiency, decompensated form, impaired

uteroplacental blood flow of the III degree. Labor premature operative at GA of 27 weeks.

Weight and body length at birth were 900 grams, 37 cm, 4/6 points on the Apgar scale. There was ALV from birth for 8 days, then respiratory support using the BNCPAP method - 6 days. He was transferred to the stage of rehabilitation at the age of 23 days of life.

Cord blood parameters at birth: CD14 + CD64 + monocytes - 38%, IL-6 - 155.5 pg/ml, IL-4 - 0.8 pg/ml.

The predictive index was calculated by the formula:

PI = -0.138×38 - 0.015×155.5 - 3.41×0.8 + 6.19 = -5.08, which is less than 0 and predicts a low risk of threshold retinopathy development.

At the age of 32 days of life, a routine ophthalmological examination was diagnosed with ROP of I degree, by 52 days of life - ROP of II stage in both eyes without subsequent progression. At the age of 70 days of life in a satisfactory condition, the child was discharged with a body weight of 2280 g.

Example 4. Premature boy G. (labor and delivery record No. 370), was born to a 35-year-old bipara woman, somatically weight down by myopia of the II degree. Gynecological anamnesis has uterine fibroids. This pregnancy, the second present, proceeded against the background of a weight down by obstetric history (medical abortion), isthmic-cervical insufficiency, chorioamnionitis, colpitis. There was delivery premature operative at 28 weeks. Weight and body length at birth 990 grams, 33 cm, 5/6 points on the Apgar scale. There was ALV from birth for 2 days of life, then respiratory support using the BNCPAP method for 3 days. He was transferred to the stage of early rehabilitation at the age of 7 days of life.

Cord blood parameters at birth: CD14 + CD64 + monocytes - 47%, IL-6 - 101.5 pg/ml, IL-4 - 0.0 pg/ml.

The predictive index was calculated by the formula:

PI = -0.138×47 - 0.015×101.5 - 3.41×0.0 + 6.19 = -1.82, which is less than 0 and predicts a high risk of the development of threshold retinopathy.

At the age of 30 days of life with a planned ophthalmological examination, ROP of stage I was diagnosed, at the age of 42 days - ROP of stage II without subsequent progression. At the age of 46 days of life in a satisfactory condition, the child was discharged with a body weight of 2021 g.

Thus, predicting the development of threshold retinopathy of prematurity by the proposed method allows to reduce the number of severe stages of ROP due to early detection of children prone to the development of the disease.

The inventive method for predicting the development of the threshold stage of retinopathy in premature infants with ELBW has the following advantages in comparison with the existing ones. The method is minimally invasive (cord blood), it allows predicting the progression of active retinopathy of premature infants on the first day of life.

5.4. Algorithm for additional examination of children born with extremely low body weight

Correlation analysis revealed positive and negative relationships between changes in the indices of innate and adaptive immunity in the blood with the development of ROP of stage III and severe BPD in children with ELBW (Fig. 1).

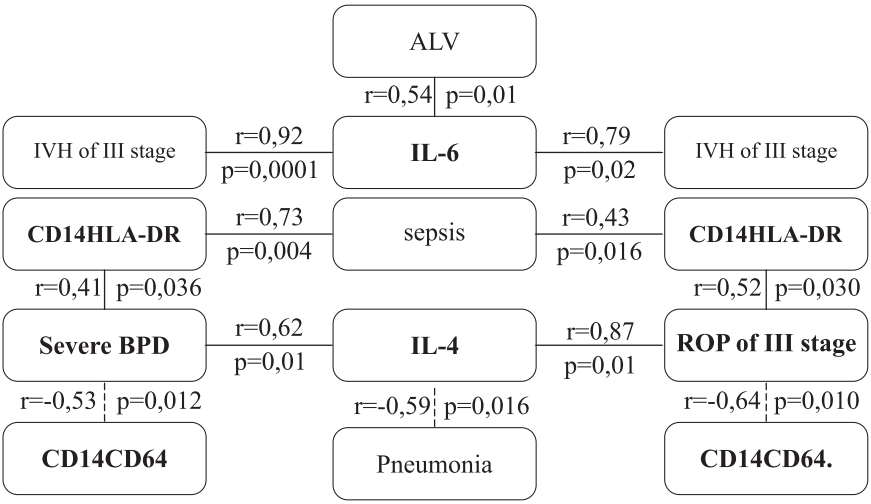

Figure 1. *Correlations between the parameters of the immune system and the presence of BPD and ROP*

Hypoxia, intrauterine infections, surfactant deficiency, genes responsible for the regulation, differentiation, growth and alveolarization of lung tissue, vasculogenesis, hyperoxygenation of the body lead to the progression of the inflammatory process at the systemic and local levels. Moreover, they have a damaging effect on the vascular-capillary network, including vessels of the retina and lungs, which affects the formation of BPD and ROP.

Immaturity of the phagocytic link of the immune system and reduced production of anti-inflammatory IL-4 predetermines the development of the infectious process. Past hypoxia and prolonged exposure to ALV causes increased production of inflammatory mediators, which have a direct effect on the membrane of alveolar capillaries, simulate immune protection, mediate acute damage to the tissues of the lungs and retina, initiating or intensifying the inflammatory cascade against the background of an infectious process, and induce freely -radical oxidation processes. The rapidly growing structures of a deeply premature baby are especially sensitive to oxidative stress, which can lead to severe tissue disorders. Later, re-

parative processes of damaged organs and hyperproduction of interstitial fibroblasts begin, leading to fibrosis and the subsequent development of BPD and ROP.

The methods developed by us, along with standard examination protocols, made it possible to recommend additional studies of newborns with ELBW to identify high-risk groups for the formation of severe postnatal pathology (Fig. 2).

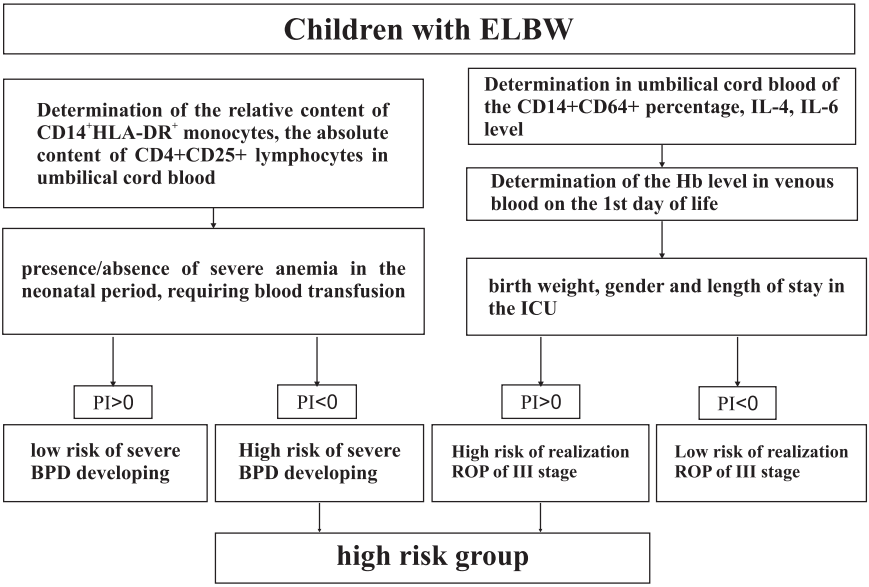

Figure 2. *Algorithm for additional examination of premature infants with ELBW in the neonatal period to predict the development of postnatal complications*

It is necessary to determine the concentration of $CD14^+HLA\text{-}DR^+$ monocytes and $CD4^+CD25^+$ lymphocytes in umbilical cord blood, taking into account the presence of severe anemia in the neonatal period, requiring repeated hemotransfusions with the subsequent calculation of the prognostic indexin case of a high risk of bronchopulmonary dysplasia in premature infants with ELBW, in order to assess the severity of this pathology.

To predict the risk of ROP of stage III for all children born with ELBW, it is recommended to determine the percentage of $CD14^+CD64^+$ monocytes, the level of IL-6 and IL-4 in the umbilical cord blood, peripheral blood hemoglobin in the first day of life, taking into account the sex of the child, body weight at birth, the length of stay in the ICU with the subsequent calculation of the prognostic index.

Our proposed algorithm for additional examination of newborns in the neonatal period makes it possible to objectively assess the tactics of nursing, timely adjust the observation pattern and prescribe adequate therapy.

NOTES

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Children with extremely low body mass: clinical characteristics, functional state of the immune system, pathogenetic mechanisms of formation of neonatal pathology

Monograph

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