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Учебное пособие

JAUNDICE SYNDROME IN CHILDREN, CRITERIA FOR POTENTIAL DANGER

Tutorial

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Представлены современные взгляды на физиологическую и патологическую гипербилирубинемия у детей. Рассмотрены этапы обмена билирубина, причины, классификация желтухи; вопросы диагностики, лечения и критерии потенциальной опасности развития желтухи у детей. Особое внимание уделено алгоритму действия врача при патологических гипербилирубинемиях у детей. Приведены обучающие тесты и задачи для закрепления изученного материала.

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ABBREVIATIONS

μmol/l/h – micromoles per liter per hour
ALAT – alanine transaminase
ASAT – aspartate transaminase
CMV – cytomegalovirus
CNS – central nervous system
FIC – famhal intraepatic cholestasis (familial intrahepatic cholestasis)
GGT – γ-glutamyl transpeptidase
GGTP – G-glutamyl transpeptidase
HAV – viral hepatitis A
Hb – hemoglobin
HBeAg – viral hepatitis B e antigen
HBsAg – viral hepatitis B s antigen
HBV – viral hepatitis B
HCV – viral hepatitis C
HDN – hemolytic disease of the newborn
NB – indirect bilirubin
Ph – Rh factor
RES – reticuloendothelial system
T3 – triiodothyronine
T4 – thyroxine
TBI – transcutaneous bilirubin index
TSH – thyroid stimulating hormone
UDGT – uridine diphosphate glucuronyl transferase

INTRODUCTION

In recent years, there has been an increase in the frequency of neonatal jaundice in the Russian Federation (by 1.5 times since 2020). Jaundice (hyperbilirubinemia) is a symptom complex accompanied by yellow staining of the skin and mucous membranes. It is a "borderline condition", most common in the neonatal period, but in most cases is physiological in nature and does not require treatment.

However, neonatal jaundice, due to the accumulation of excess bilirubin in the blood, sometimes requires urgent treatment. Indirect bilirubin is a neurotoxic poison and under certain conditions (prematurity, hypoxia, hypoglycemia, prolonged exposure, etc.) causes a specific lesion of the subcortical nuclei and the cerebral cortex – bilirubin encephalopathy. According to various data, in the first week of life, jaundice occurs in 25–50 % of full-term and 70–90 % of premature newborns. The significance of the increase in the incidence of neonatal jaundice is increasing due to the recent increase in the population of mental retardation of children and the pathology of the nervous system. In recent years, there has been an increase in the frequency of neonatal jaundice in the Russian Federation (by 1.5 times since 2020). Jaundice (hyperbilirubinemia) is a symptom complex accompanied by yellow staining of the skin and mucous membranes. It is a "borderline condition", most common in the neonatal period, but in most cases is physiological in nature and does not require treatment.

With an increase in the frequency of neonatal jaundice, primarily conjugative, as well as hemolytic disease of the newborn, the problem of the so-called protracted jaundice, detected in children older than 1 month of age, is increasingly heard. Information about the role of various etiological factors contributing to an increase in the frequency of neonatal jaundice in the literature is very scattered. According to some data, this is facilitated by an increase in the number of premature babies, newborns with intrauterine growth retardation, with morphofunctional immaturity, who have undergone acute or chronic hypoxia, and were born to mothers with endocrine and other somatic pathologies. Probably, a certain contribution to the increase in the frequency of neonatal jaundice is made by an increase in the number of children with intrauterine infections (primarily TORH, hepatitis).

A pediatrician needs to know the main features of bilirubin metabolism in newborns, clinical and laboratory criteria for physiological and pathological jaundice, as well as criteria for the potential danger of hyperbilirubinemia in order to timely identify deviations from the "normal"

course of neonatal jaundice and decide on the need for outpatient or inpatient examination and treatment.

Children who have undergone severe hyperbilirubinemia require a correct assessment of the prognosis of further development and observation with rehabilitation measures by outpatient pediatricians and other specialists.

1. EXCHANGE OF BILIRUBIN

1.1. Stages of bilirubin metabolism

I stage. In macrophages of the liver, spleen and bone marrow, under the influence of the heme oxygenase enzyme and with the participation of oxygen and the NADPH coenzyme, hemoglobin is split into 4 main components: globin, iron, carbon monoxide and linear tetrapyrrole (or IX α -biliverdin).

II stage. The cytosolic enzyme biliverdin reductase transforms IX α -biliverdin into the fat-soluble substance IX α -bilirubin (free or unconjugated or indirect bilirubin), which is lipid-soluble but water-insoluble.

III stage. Indirect bilirubin formed in macrophages in a free state enters the blood, where it binds strongly to albumin and is transported to the sinusoids of the liver (1 g of albumin can bind from 1 to 8.2 mg of bilirubin).

IV stage. In the sinusoids of the liver at the level of the hepatocyte membrane, unconjugated (indirect) bilirubin is separated from albumin and diffuses with the help of transport proteins through the water layer surrounding the hepatocyte and the cytomembrane into the hepatocyte.

V stage. In hepatocytes, under the influence of the microsomal enzyme uridine diphosphate glucuronyl transferase (UDGT), unconjugated (indirect) bilirubin binds (conjugates) with glucuronic acid, and to a much lesser extent with sulfates, xylose, and glucose. Bilirubin mono- and diglucuronide are formed (conjugated or direct, or bound water-soluble bilirubin). The formation of direct bilirubin requires the presence of oxygen and glucose.

VI stage. Conjugated (direct) bilirubin is secreted into the lumen of the bile capillaries and, as part of bile, after passing through the bile ducts, enters the gallbladder and intestines.

VII stage. In the large intestine, conjugated (direct) bilirubin undergoes hydrolysis to form urobilinogen (free bilirubin). Part of the urobilinogen is reabsorbed in the intestine and re-enters the blood (this pathway is called the enterohepatic recirculation of bilirubin). (See Application No. 1).

1.2. Features of bilirubin metabolism in newborns

Bilirubin in the fetal body practically does not undergo conjugation, since there are no proteins in the liver that ensure the capture of bilirubin by

hepatocytes, and the activity of uridine diphosphate glucuronyl transferase is inhibited by maternal hormones. The main organ that removes bilirubin from the fetus is the placenta, through which bilirubin enters the mother's bloodstream, where it undergoes further utilization.

During the neonatal period, the binding of bilirubin to albumin is reduced, especially in premature babies, the conjugation and transport of bilirubin in the liver is slowed down, and the reabsorption of bilirubin (enterohepatic recirculation) in the intestine is increased. The increase in reabsorption of bilirubin in the intestine is due to the predominance of bilirubin monoglucuronides in the newborn, which are more easily hydrolyzed compared to diglucuronide. In the intestines of newborns, the concentration of glucuronidase, which causes hydrolysis, is also increased, and there is a deficiency of bacterial intestinal flora, under the influence of which bilirubin is catabolized into urobilinogen and stercobilin.

A consequence of the peculiarities of the bilirubin metabolism of the newborn is the development of a number of conditions that are characteristic of the neonatal period:

1. The development of physiological jaundice for 2–5 days of life.
2. In low birth weight newborns, jaundice may persist for up to 2 weeks or more. Perhaps short-term discoloration of feces, the presence of direct bilirubin in the urine due to transient cholestasis.
3. The intensity of jaundice in newborns increases with hypoxia and hypoglycemia, as well as with the appointment of water-soluble analogues of vitamin K.
4. With a high level of free (non-conjugated, indirect) bilirubin in the blood serum, there is a threat of developing bilirubin encephalopathy (nuclear jaundice), which occurs exclusively in the neonatal period.

1.3. Causes of pathological hyperbilirubinemia

Hyperbilirubinemia – an increase in the concentration of total bilirubin in the blood serum above the norm.

Jaundice – a visual manifestation of an elevated level of bilirubin in the blood:

- a) in full-term newborns appears when the level of bilirubin is more than 67 $\mu\text{mol/l}$;
- b) in premature babies – more than 120 $\mu\text{mol/l}$.

Causes of pathological hyperbilirubinemia:

- ▶ hyperproduction of bilirubin due to hemolysis of erythrocytes (erythro- and hemoglobinopathies, extensive hemorrhages);
- ▶ impaired conjugation of bilirubin in hepatocytes – hepatic (conjugation) jaundice;
- ▶ combined violation of conjugation and excretion – hepatic jaundice;
- ▶ impaired excretion of bilirubin into the intestine – obstructive jaundice;
- ▶ increased intestinal reabsorption (pyloric stenosis, intestinal paresis).

Pathological hyperbilirubinemia:

- early (up to 24 hours of life) or late (at 2 weeks) appearance, long-term persistence (more than 3 weeks), "wavy" course;
- pale or greenish skin tone;
- general deterioration;
- dark urine, discolored stools;
- total blood bilirubin $>256 \mu\text{mol/l}$ in term and $>171 \mu\text{mol/l}$ in preterm;
- direct fraction of bilirubin $>20 \%$.

2. CLASSIFICATION

2.1. Jaundice classification

Due to the existence of two fractions of bilirubin (direct or bound and indirect or free), as well as many causes that can cause hyperbilirubinemia, there are several classifications of jaundice. The most common are the classification according to the level of bilirubin metabolism disorder (prehepatic jaundice, hepatic or hepatocellular, subhepatic) and according to the content of bilirubin fractions (unconjugated or indirect, conjugated or direct).

Classification of neonatal jaundice

Given the variety of causes of hyperbilirubinemia in newborns, there are many classifications of neonatal jaundice. So, all jaundices can be divided into physiological (up to 90 % of newborn jaundices) and pathological (10 % of all jaundices). By genesis, all jaundices are divided into hereditary and non-hereditary, congenital and acquired. According to laboratory data, all neonatal jaundices are divided into hyperbilirubinemia with a predominance of indirect bilirubin (NB) and hyperbilirubinemia with a predominance of direct bilirubin.

The most informative is the pathogenetic classification. It relies on four main mechanisms for the development of pathological hyperbilirubinemia:

- 1) hyperproduction of bilirubin (most often due to hemolysis);
- 2) reduced clearance of bilirubin due to:
 - a defect in the capture of bilirubin by the hepatocyte;
 - disorders of bilirubin conjugation in hepatocytes;
 - a defect in the excretion of bilirubin from the hepatocyte;
- 3) impaired excretion of bilirubin into the intestine (mechanical jaundice);
- 4) combined violation of conjugation and excretion.

Most often, the pathogenetic classification of neonatal jaundice is used in practice (Shabalov N. P., 2020).

Hereditary	Acquired
Increased production of bilirubin	
Erythrocyte membranopathies (microspherocytosis, etc.)	HDN
Erythrocyte enzyme deficiencies (glucose-6-phosphate dehydrogenase, etc.)	Blood sequestration
Hemoglobinopathies	Swallowed Blood Syndrome
	Polycythemia
	Drug hemolysis
	Increased enterohepatic circulation of bilirubin (pyloric stenosis, intestinal obstruction)
Decreased clearance of bilirubin	
Bilirubin uptake defect by hepatocytes (b. Gilbert)	Hormone deficiencies (hypothyroidism, hypopituitarism) or excess (maternal milk jaundice)
Conjugation defects (c. Crigler – Najjar types 1 and 2, Lucey – Driscoll)	Hepatitis (infectious, toxic)
Defects in the excretion of bilirubin from the hepatocyte (p. Dubin – Jones, Rotor)	Total parenteral nutrition
Symptomatic (hypothyroidism, galactosemia, etc.)	
Obstructive (mechanical) jaundice	
Atresia or hypoplasia of the extrahepatic biliary tract of the fetal type – syndromic anomalies of the biliary tract in combination with other congenital malformations (Alagille syndrome, trisomy 13, 18, 21 pairs of chromosomes)	Atresia or hypoplasia of the extrahepatic biliary tract due to perinatal hepatitis
Familial non-syndromic cholestasis (Byler, McElfresh)	Intrahepatic atresia and hypoplasia of the biliary tract in perinatal hepatitis, cirrhosis
Symptomatic cholestasis (cystic fibrosis, α 1-antitrypsin deficiency, etc.)	Stenosis or cyst of the common bile duct
	Choledocholithiasis
	Compression by tumors
	cholestasis syndrome
Mixed jaundices	
Transient (physiological) jaundice of newborns	
Neonatal jaundice of prematurity	
Sepsis	

2.2. Clinical manifestations of icteric syndrome depending on pathogenetic mechanisms

Clinical and laboratory signs of suprahepatic jaundice:

- develops with hemolysis and hereditary disorders of bilirubin metabolism;
- the level of bilirubin in the blood serum is increased mainly due to the fraction of free bilirubin;
- the activity of serum transaminases (ALAT and ASAT), alkaline phosphatase remains within the normal range;
- bilirubin is not determined in the urine;
- often there is hepatosplenomegaly.

Clinical and laboratory signs of hepatic (hepatocellular) jaundice:

- develops with hepatitis, sepsis, toxic damage to the liver (for example, in case of poisoning with pale toadstool);
- the level of bilirubin in the blood serum is increased due to two fractions: free and bound (the level of bound bilirubin is more than 30 % of the total amount of bilirubin);
- increased activity of transaminases;
- the feces are discolored;
- there are signs of liver failure of varying severity;
- can develop very quickly (within a few hours);
- consciousness is disturbed from minor changes in mental status to confusion, coma, the appearance of a “flapping” tremor;
- weakness and fatigue;
- there are bruises (spontaneous and after venipuncture);
- fluid retention (from weight gain to edema and ascites);
- often hepatosplenomegaly.

Clinical and laboratory signs of subhepatic (cholestatic) jaundice:

- develops with various congenital and acquired diseases, accompanied by the development of cholestasis (for example, with atresia of the biliary tract);
- increased direct (conjugated or bound) bilirubin in the blood (more than 15 % of total bilirubin);
- jaundice progresses and has a greenish tint;
- increased level of alkaline phosphatase;
- conjugated bilirubin is determined in urine;
- the feces are discolored;
- skin itching is noted;

- develops malabsorption syndrome (steatorrhea);
- in chronic cholestasis osteodystrophy progresses;
- trihydroxy bile acids appear in the blood;
- impaired adaptation of the eye to the dark ("night blindness");
- the level of serum lipoproteins is increased;
- appear xanthomas and xanthelasma (deposition of cholesterol in the skin);
- increased skin pigmentation;
- reduced body weight;
- accumulates copper in the liver;
- hepatosplenomegaly.

2.3. Etiology of unconjugated (indirect) hyperbilirubinemia in newborns (Depending on the time of occurrence)

Indirect bilirubin level is more than 85 % of total bilirubin.

- a) From the moment of birth to the 2nd day of life – hemolytic disease of the newborn (HDN);
- b) 3–7 days of life – physiological hyperbilirubinemia;
- c) 1–8 weeks of life:
 - congenital hemolytic anemia;
 - jaundice of breast milk;
 - Lucea – Driscoll syndrome (transient familial hyperbilirubinemia);
 - Crigler – Najjar hyperbilirubinemia;
 - hypothyroidism;
 - cephalohematoma;
 - sepsis;
 - pyloric stenosis.

3. THE MOST COMMON CAUSES OF INDIRECT HYPERBILIRUBINEMIA IN NEWBORN

3.1. Jaundice due to increased production of bilirubin (suprahepatic)

All hemolytic jaundices are characterized by the presence of a symptom complex, including jaundice on a pale background (lemon jaundice), an enlarged liver and spleen, an increase in the level of indirect bilirubin in the blood serum, normochromic anemia of varying severity with reticulocytosis. The severity of the child's condition is always due not only to bilirubin intoxication, but also to the severity of anemia.

3.1.1. Prehepatic jaundice (hemolytic). Pathogenesis

Under the influence of pathological factors on erythrocytes and reticuloendothelial system (RES) organs, a significantly accelerated (pathological !!!) breakdown of erythrocytes (hemolysis) occurs, which ultimately leads to a rapid increase in the concentration of unbound bilirubin in the blood plasma.

With a rapid increase in the concentration of unbound bilirubin, relative liver failure develops, hepatocytes significantly increase their conjugating function, but they cannot cope with the entire volume of unbound bilirubin formed. Most of the unbound bilirubin remains in the blood plasma and its concentration increases. The concentration of conjugated bilirubin in bile, formed as a result of increased conjugating function of the liver, also increases. In the small intestine, the concentration of the formed stercobilinogen and urobilinogen increases.

1. As a result of a high concentration of stercobilinogen in the feces, its color becomes intensely dark brown.

2. The concentration of urobilinogen in the venous blood of the small intestine, and then in the portal vein system, increases significantly.

3. Hepatocytes do not capture urobilinogen from the blood as before (as a result of the developed relative liver failure, they cannot even capture all the unbound bilirubin), it penetrates the hepatic veins, and then reaches the kidneys and urine, staining it in the color of "dark beer".

4. In the biochemical analysis of blood, an increase in the concentration of total bilirubin is noted due to an increase in the concentration of both fractions, mainly due to unbound bilirubin.

5. In the clinical analysis of blood, chronic anemia is noted due to the acceleration of hemolysis and the developed relative (or absolute) insufficiency of the function of the hematopoietic system.

3.1.2. Hereditary hemolytic jaundices

Hereditary hemolytic jaundice is characterized by a delayed (after 24 hours of life) appearance of clinical and laboratory signs inherent in HDN, as well as a change in the shape and size of erythrocytes during the morphological examination of a blood smear, a violation of their osmotic stability.

In addition, anamnestic data are important (familial icteric syndrome, anemia, usually occurring against the background of provoking factors, structural features of the skeleton, dysembryogenesis stigmas), as well as the presence of progressive anemia, often reaching a severe degree.

Hereditary hemolytic anemias are of great variety. The most common of these is *microspherocytic hemolytic Minkowski – Choffard anemia*. The defective gene is located on the 8th pair of chromosomes. The result of the mutation is the production of abnormal erythrocytes that are spherical and smaller (less than 7 nm) in size, subject to excessive destruction in the crypts of the spleen. The anamnesis is characterized by the presence in the family of relatives with a similar disease. The diagnosis is confirmed by the detection of microspherocytic erythrocytes, a shift in the Price-Jones curve to the left, a decrease in the osmotic stability of erythrocytes, a change in the sphericity index and the average concentration of hemoglobin in erythrocytes. The disease proceeds in waves, hemolytic crises are accompanied by fever, loss of appetite and vomiting. Crises are usually provoked.

During the neonatal period, another type of hereditary hemolytic anemia can be detected, characterized by a change in the shape of red blood cells – *the so-called infantile pycnocytois*. The first signs of the disease appear in the first week of life and more often in premature babies. Red blood cells in a stained blood smear have spiny processes. In addition to anemia, edema and thrombocytosis are also detected. The appointment of vitamin E at a dose of 10 mg/kg per day leads in most cases to clinical and laboratory remission.

Blood smear examination of newborns may also reveal target red blood cells, which is typical for *hemoglobinopathies* (thalassemia, sickle cell anemia). Sickle cell anemia is more common in residents of Central Asia, Azerbaijan and Armenia and manifests itself in the neonatal period only in homozygous carriers of s-hemoglobin.

Diagnosis of *hereditary enzymopenic anemias* (deficiency of glucose-6-phosphate dehydrogenase, pyruvate kinase, hexogenase, 2,3-diphosphoglyceromutase, phosphohexoisomerase) in newborns is extremely rare, as it requires highly differentiated studies. In the clinical picture in newborns with this pathology, hemolytic anemia with reticulocytosis, an enlarged liver and spleen are detected. A family history is characteristic.

3.1.3. Acquired hemolytic jaundices

3.1.3.1. Hemolytic disease of the newborn (HDN)

In 1900, Landsteiner found that a person has 4 blood groups. Blood groups are inherited by three allelic genes O, A, B. Gene A dominates the O and B genes, gene B dominates the O gene. Group antigens are located on the outer surface of the erythrocyte membrane and are detected as early as 5–6 weeks of gestation. Antigens A and B are contained not only on erythrocytes, but also in all tissues of the fetus, amniotic fluid and the amniotic membrane of the placenta. The fetus is affected by group antigens (according to the ABO system) 2–3 times more often than others (1 in 140 births).

Among the many reasons that contribute to an increase in the level of bilirubin in the blood, hemolytic disease of the newborn (HDN), which occurs when the group (ABO) or Ph-incompatibility of the mother and fetus is of great importance. TTH is based on the transport of maternal antibodies (immunoglobulins G3) to fetal erythrocytes through the placenta. As a rule, HDN due to Ph-incompatibility is more severe.

ABO-incompatibility, being the main cause of HDN, is milder. However, cases of atypical severe course of HDN due to ABO-incompatibility, accompanied by hepatosplenomegaly, hemagglobinuria, thrombocytopenia, and the development of renal failure, have been described.

Thrombocytopenia, with which renal thrombosis is associated, is very common in low birth weight infants. In the vast majority of newborns, HDN

due to ABO-incompatibility is mild, its severity depends on the newborn's belonging to an ethnic group. Only 0,33–2,2 % of newborns with ABO-incompatibility have signs of disease manifestation. The main manifestation of ABO-incompatibility is hyperbilirubinemia, when the appointment of phototherapy leads to a rapid positive effect. Severe hyperbilirubinemia is usually associated with anemia. Unfortunately, in recent years, HDN due to ABO-incompatibility in maternity hospitals has not been diagnosed in a timely manner. The severity of the condition of a newborn with HDN due to Ph-incompatibility depends on the duration of intrauterine sensitization. For the occurrence of HDN, it is not enough only the penetration of fetal antigens into the maternal body. A normal placenta performs a protective function, the antibodies (globulin fractions) in it neutralize incoming antigens from the fetal body. An increase in the sensitization of the mother's body occurs when the integrity of the placental barrier is violated due to vascular or degenerative changes in the placenta. Of great importance in Ph-incompatibility is the preliminary sensitization of the mother as a result of repeated abortions performed after 10–14 weeks of pregnancy. Thanks to immunoprophylaxis carried out during pregnancy, the number of newborns with severe HDN due to Ph-incompatibility has significantly decreased. The main features of HDN according to ABO and Ph-incompatibility are given in Table. 1 (Application No. 2).

Clinical criteria for HDN:

- 1) appears in the first 24 hours after birth (usually the first 12 hours);
- 2) increases during the first 3–5 days of life;
- 3) begins to fade from the end of the first to the beginning of the second week of life;
- 4) disappears by the end of the third week of life;
- 5) skin in ABO-conflict, as a rule, is bright yellow, with Rh-conflict it can have a lemon tint (jaundice on a pale background);
- 6) the general condition of the child depends on the severity of hemolysis and the degree of hyperbilirubinemia (from satisfactory to severe);
- 7) in the first hours and days of life, as a rule, there is an increase in the size of the liver and spleen;
- 8) usually – normal color of feces and urine, against the background of phototherapy, there may be a green color of the stool and a short-term darkening of the urine.

Laboratory criteria for HDN:

- 1) the concentration of bilirubin in cord blood (moment of birth) – with mild forms of immunological conflict in Rh and in all cases of

ABO-incompatibility – $\leq 51 \mu\text{mol/l}$; in severe forms of immunological conflict for Rh and rare factors – significantly higher than $51 \mu\text{mol/l}$;

2) the concentration of hemoglobin in cord blood in mild cases is at the lower limit of normal, in severe cases it is significantly reduced;

3) hourly increase in bilirubin in the first day of life is more than $5.1 \mu\text{mol/l/hour}$, in severe cases – more than $8.5 \mu\text{mol/l/hour}$;

4) maximum concentration of total bilirubin on days 3–4 in peripheral or venous blood: $>256 \mu\text{mol/l}$ in full-term babies, $>171 \mu\text{mol/l}$ in premature babies;

5) total blood bilirubin increases mainly due to the indirect fraction;

6) the relative proportion of the direct fraction is less than 20 %;

7) decrease in hemoglobin level, erythrocyte count and increase in the number of reticulocytes in clinical blood tests during the 1st week of life.

Preventive actions to prevent the development of hemolytic disease of the newborn, which should be carried out already in the antenatal clinic, they consist in registering all women with Rh-negative and O (I) blood groups, clarifying the history data in terms of the presence of a sensitization factor, determining the level of Rh antibodies and if necessary, early delivery. All women with Rh-negative blood on the first day after birth are shown the introduction of anti-D-globulin.

As a rule, the diagnosis of HDN is established in the maternity hospital. However, the district pediatrician needs to analyze the history data, clinical and laboratory signs, since not always the diagnosis of HDN can be made at the stage of the maternity hospital. It should not be forgotten that a conflict in the ABO system is possible not only if the mother has O (I) blood groups, but the child has A (II) blood groups. Incompatibility is possible in all cases when the child has a paternal antigen that is absent from the mother. Therefore, if HDN is suspected, especially in a child who has been breastfed since birth, an inpatient examination is necessary. With further clinical examination of children with HDN and, especially, vaccination, it must be remembered that these children suffered an immune conflict in the perinatal period.

3.1.3.2. Jaundice in hemorrhages

Cephalohematomas, subdural hematomas, ecchymosis, hemangiomas can be the cause of a high bilirubin content due to a large number of damaged red blood cells. This phenomenon is also observed in other hemorrhages. Hyperbilirubinemia is observed in newborns who received intrauterine blood transfusion due to delayed absorption of intraperitoneal blood.

Removal of erythrocytes during peritoneal lavage helps to slow down the production of bilirubin.

In newborns with cephalohematoma or widespread subcutaneous ecchymosis, the increase in jaundice (indirect bilirubin) can be very significant. It has been established that 1 g of hemoglobin is a source of 35 mg of bilirubin. At a hemoglobin concentration in the peripheral blood of 200 g/l (which is not uncommon for a newborn), every 10 ml of blood contains 2 g of hemoglobin. Thus, a hemorrhage (cephalohematoma) with a volume of 10 ml can become a source of 70 mg of bilirubin.

3.1.3.3. Increased enterohepatic circulation of bilirubin

1 gram of meconium contains approximately 1 mg of bilirubin, and its total amount is 100–200 mg. Violation of the passage of contents through the intestines (Hirschsprung's disease, intestinal atresia, stenosis, meconium plug or ileus) increase the level of bilirubin in the blood due to an increase in enterohepatic circulation. Jaundice in these cases rarely develops in the first 24 to 48 hours of a child's life.

3.2. General clinical and laboratory signs of suprahepatic jaundice

The main symptom is an increase in total bilirubin due to indirect bilirubin.

1. Total bilirubin rarely exceeds 90 $\mu\text{mol/L}$.
2. Pleiochromia (increased content of bile pigments in bile).
3. Anemia.
4. Increase in the number of reticulocytes (immature erythrocytes) (increased erythrocyte regeneration).
5. An important clinical sign is the absence of acholia, on the contrary, the dark color of feces and urine is characteristic (increased content of stercobilinogen and urobilinogen).

3.3. Algorithm of the action of the primary care physician in case of suprahepatic jaundice

1. Clinical blood test (Hb level, reticulocytes).
2. Urinalysis (presence of urobilin).

3. Analysis of feces for the presence of stercobilin.
4. Biochemical blood test (study of total bilirubin, free bilirubin, indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltranspeptidase, total protein, protein fractions, alpha-amylase).
5. Blood test for the presence of antibodies to hepatitis A, B and C viruses.
6. Ultrasound examination of the abdominal organs.
7. Consultation of a hematologist, if necessary, hospitalization of the patient.

3.4. Bilirubin encephalopathy in newborns

Neurons in the process of maturation and differentiation are extremely susceptible to the effects of indirect bilirubin. The penetration of indirect (fat-soluble) bilirubin into the brain tissue leads to its accumulation in the basal ganglia and the development of bilirubin encephalopathy (kernicterus) in newborns. Morphologically, in nuclear jaundice, bilirubin deposits are found in the gray matter of the basal ganglia, cerebellum, medulla oblongata and hypothalamic centers, staining of the visceral membranes of internal organs. Late stages of bilirubin encephalopathy are characterized by gliosis and destruction of neurons in the basal and subthalamic nuclei. In premature infants, such changes can be detected in the absence of characteristic clinical symptoms and a relatively low level of indirect bilirubin in the blood.

Factors contributing to the development of bilirubin encephalopathy in newborns:

- hypoalbuminemia;
- increase in the level of free fatty acids in the blood serum;
- hypoglycemia;
- acidosis;
- hypoxic-ischemic damage to the central nervous system;
- infusion of fat emulsions;
- accumulation of organic anions in the blood (free bile acids, hematin, salicylates, sulfonamides);
- sepsis.

3.4.1. Critical level of bilirubin for the development of kernicterus

Due to the fact that the threshold of sensitivity of neurons to bilirubin is lowered in premature or low birth weight infants, there are differences in the definition of the critical level for full-term and premature newborns:

- in premature and low-birth-weight newborns (weighing less than 2500.0 g), specific therapy is indicated at a bilirubin level of 170 $\mu\text{mol/l}$ and above;

- in full-term newborns with normal weight, specific therapy is indicated at a bilirubin level of 255 $\mu\text{mol/l}$ and above.

Critical levels of bilirubin are 170 $\mu\text{mol/L}$ for preterm infants and 306 $\mu\text{mol/L}$ for full-term infants.

3.4.2 Clinical manifestations of kernicterus (bilirubin encephalopathy)

There are acute and chronic forms of kernicterus.

A. Acute form.

Phase 1 (first 2 days of life): CNS (central nervous system) depression, decreased spontaneous motor activity, muscle hypotension, weakened sucking reflex, apnea, asphyxia.

Phase 2 (middle of the first week of life): hypertonicity, fever, opisthotonus, piercing "brain" cry, spasm of the gaze, a symptom of the "setting sun".

Phase 3 (after the first week of life): spastic paresis, oculomotor and vestibular disorders, hearing loss, mental retardation, the formation of cerebral palsy.

Preterm infants, as a rule, do not have stages of development of bilirubin encephalopathy, they are characterized by depression, muscle hypotension, and nonspecific symptoms.

B. Chronic form.

During the first year of life, children have hypotension, increased tendon reflexes, hypertonicity of the neck muscles, and a delay in the development of motor skills.

After the first year of life, uncoordinated movements (choreoathetosis, movement in the form of sharp twitches or tremors, tremors), eye rolling, sensory neurological hearing loss are characteristic. (Application No. 3).

4. JAUNDICE DUE TO REDUCED BLIRUBIN CLEARANCE (CONJUGATIVE JAUNDICE)

Conjugative jaundices due to a predominant violation of bilirubin conjugation in hepatocytes. The most common cause of conjugative hyperbilirubinemia in newborns is a discrepancy between the normal production of bilirubin and an imperfect system for its excretion from the body due to the immaturity of the liver enzyme systems. These include jaundice of apparently healthy premature and immature newborns, jaundice in diabetic fetopathy and congenital hypothyroidism, jaundice in high intestinal obstruction, etc. Severe disorders of bilirubin conjugation are observed in a number of hereditary diseases: familial transient hyperbilirubinemia of the Arias-Lucey-Driscoll type, Crigler – Najjar syndrome, Gilbert's syndrome.

Conjugative jaundice, the main signs:

1. Onset – usually not earlier than 24 hours of age.
2. Grow after 4 days.
3. Do not fade until the end of the 3rd week.
4. Generally good condition.
5. Orange skin tone.
6. No enlargement of the liver, spleen.
7. The usual color of feces, urine (with the exception of Crigler – Najjar syndrome).
8. In the KLA – Hb, E, reticulocytes – normal.
9. Total blood bilirubin on days 3–4 $> 255 \mu\text{mol/l}$ in full-term babies, $> 171 \mu\text{mol/l}$ in preterm babies up to 35 weeks.
10. Direct bilirubin $< 20 \%$.

Causes of conjugative jaundice:

- Children of mothers with DM.
- Hereditary diseases: s-m Gilbert, Crigler – Najjar.
- Jaundice from mother's milk.
- Hypothyroidism.
- Hyperbilirubinemia of prematurity.
- Side effects of drugs.

Laboratory Criteria conjugative jaundice:

- 1) the concentration of bilirubin in cord blood (the moment of birth) is less than $51 \mu\text{mol}$;
- 2) the concentration of hemoglobin in cord blood is normal;

- 3) hourly increase in bilirubin in the first day of life is less than 6,8 $\mu\text{mol/l/hour}$;
- 4) maximum concentration of total bilirubin on days 3–4 in peripheral or venous blood: > 256 $\mu\text{mol/l}$ in full-term babies, >171 $\mu\text{mol/l}$ in premature babies;
- 5) total blood bilirubin increases due to the indirect fraction;
- 6) the relative proportion of the direct fraction is less than 10 %;
- 7) normal values of hemoglobin, erythrocytes and reticulocytes in clinical blood tests).

4.1. Hereditary conjugative jaundices

4.1.1. Gilbert's syndrome

Frequency. From 2 to 6 % in the population. Boys get sick 2–4 times more often than girls.

Type of inheritance: autosomal dominant with varying degrees of penetrance. Often associated with glucose-6-phosphate dehydrogenase deficiency. In this case, there is a more severe and prolonged course of jaundice, bilirubin can reach critical numbers.

Pathogenesis. The development of the disease is due to a defect in the sinusoidal membrane of the hepatocyte with a violation of the intracellular transport of bilirubin and a decrease in the activity of conjugation processes up to 50 % of the norm.

Clinic. In the neonatal period, jaundice proceeds as physiological and does not cause alarm among doctors. The disease is usually diagnosed at school or adolescence.

Laboratory diagnostics. In the neonatal period is difficult. The diagnosis is made, as a rule, when other types of jaundice are rejected.

4.1.2. Crigler – Najjar syndrome (two types)

1st type. Type of inheritance: autosomal recessive.

Etiopathogenesis. The development of the disease is due to the absence of the enzyme glucuronyl transferase in the liver.

Clinic. Jaundice appears in the first hours of life, there is a rapid and steady increase in bilirubin (up to 500–700 $\mu\text{mol/l}$ and above), which persists for life. The development of nuclear jaundice is characteristic. The

stool is acholic, there are defects in the tooth enamel. There is no effect from the appointment of phenobarbital. Phototherapy and exchange transfusion provide only a short-term decrease in bilirubin levels. Children usually die in the first year of life from kernicterus.

2nd type. Type of inheritance: autosomal dominant. Bilirubin conjugation defect is usually noted in one of the parents.

Etiopathogenesis. The disease is based on a sharp decrease (up to 5–10 % of the norm) of glucuronyl transferase activity of the liver.

Clinic. Neonatal jaundice is not so severe, the level of bilirubin usually does not exceed 350–380 $\mu\text{mol/l}$, kernicterus develops less frequently and only in the neonatal period. Stools and urine are light in the first days of life, but after a few days they acquire a normal color. In bile, bilirubin-monoglucuronide is detected (inhibition of conjugation at the 2nd stage of conjugation). With the appointment of phenobarbital, jaundice decreases, but after discontinuation of the drug, it recurs again.

4.1.3. Lucea – Driscoll syndrome

Type of inheritance: autosomal recessive.

Etiopathogenesis. The blood serum of mothers of such children contains an inhibitor of glucuronyl transferase activity (probably one of the pregnancy hormones).

Clinic. Jaundice develops in the first days of life. Hyperbilirubinemia can be severe and lead to the development of kernicterus. With timely treatment, the prognosis is favorable.

4.1.4. Dubin – Jones syndrome

Type of inheritance: autosomal recessive.

Etiopathogenesis. The disease is based on a deficiency of canalicular secretion of bilirubin from the hepatocyte.

Clinic. Rarely diagnosed in the neonatal period. It is characterized by moderate jaundice and a slight increase in the liver.

Laboratory diagnostics:

1. Biochemical blood test. Hyperbilirubinemia is revealed with a predominance of direct bilirubin.

2. General analysis of urine – coproporphyruria.

3. Liver biopsy. In Dubin – Johnson syndrome, brown-black inclusions are found, granules resembling melanin (lipofuscin). In Rotor syndrome, pigment accumulation in the liver is not detected.

4.1.5. Metabolic disorders

a) Galactosemia – a violation of galactose metabolism caused by congenital deficiency of galactokinase, galactose epimerase or galactose-1-phosphate uridylyltransferase. With this disease, the conjugation process is first disturbed, and then the excretion of bilirubin.

Clinic. From the first day of life marked, persistent jaundice. At first, indirect bilirubin predominates, then the proportion of direct bilirubin increases. Hepatosplenomegaly is always pronounced, liver failure develops by the end of the neonatal period. Symptoms of the underlying disease are vomiting, diarrhea, refusal to feed. Characterized by hemolysis, due to a decrease in the osmotic stability of erythrocytes, hemorrhagic syndrome can be observed.

Laboratory diagnostics.

1. Biochemical blood test. First, unconjugated bilirubin grows, and then direct bilirubin.

2. The osmotic resistance of erythrocytes is reduced.

3. Determination of galactose in urine, blood. Her levels are up.

4. Determination of galactose-1-phosphate and galactose-1-phosphate-uridylyltransferase in erythrocytes.

b) Fructosemia

It proceeds more benignly than galactosemia.

Diagnostics. It based on the determination of fructose in urine and blood.

4.2. Acquired conjugative jaundices

4.2.1. Jaundice from mother's milk

Jaundice from mother's milk diagnosis of exclusion of other causes of jaundice – the maximum level of bilirubin does not exceed 250 $\mu\text{mol/l}$. Exclusive breastfeeding is characteristic; the presence of indirect hyperbilirubinemia; good weight gain, normal neuropsychic development; there are no signs of hemolysis, enlargement of the liver, spleen, when breastfeeding is stopped for a short time, the level of bilirubin drops sharply and after the resumption of breastfeeding does not exceed 80–85 $\mu\text{mol/l}$ with complete normalization by 4–6 weeks of life.

Frequency: 1 in 50–200 newborns (0,5–2 %) who are breastfed.

Etiopathogenesis. The causes of the disease are heterogeneous. This:

- lower calorie content of food with natural feeding in the first days of life (due to unsteady lactation);
- increased levels of pregnandiol in human milk;
- high activity of lipoprotein lipase in milk;
- elevated levels of free fatty acids;
- the presence of beta-glucuronidase in human milk.

The leading pathogenesis is currently considered to be a violation of excretion, and not conjugation of bilirubin.

Clinic. Jaundice begins as physiological (on the 3rd day of life), but is characterized by a protracted course. The peak of the rise in bilirubin falls on the 6th – 15th days of a child's life, the maximum level of total bilirubin rarely exceeds 200–250 $\mu\text{mol/l}$, the duration of jaundice is up to 9 weeks.

Diagnostics. Termination of breastfeeding and transfer of the child to feeding with adapted mixtures for 48–72 hours (there should be a decrease in the level of total bilirubin by 85 $\mu\text{mol/l}$ or more). After 4–6 days after cancellation, breastfeeding can be resumed, because repeated jaundice, as a rule, does not increase or increases slightly.

Despite the long-term persistence of icteric coloration of the skin, with jaundice from mother's milk, it is not advisable to stop breastfeeding. It should be emphasized that the level of bilirubin less than 20,8 mg % (354 $\mu\text{mol/l}$) in healthy full-term newborns does not adversely affect the development of the child.

4.2.2. Jaundice in hypothyroidism

Frequency. It occurs in 70–80 % of children suffering from congenital hypothyroidism.

Etiopathogenesis. The occurrence of jaundice is due to a deficiency of thyroid hormones, which contribute to the maturation of the enzyme glucuronyl transferase. In addition, the skin of children with hypothyroidism is able to retain bilirubin.

Clinic. Prolonged jaundice is characteristic. It occurs on 2–3 days of life and lasts from 3–12 to 16–20 weeks. Accompanied by symptoms of hypothyroidism (moderate edematous syndrome, lethargy, adynamia, rough voice, marbled and dry skin). The appointment of thyroid hormones leads to the normalization of bilirubin levels.

Laboratory diagnostics:

1. Biochemical blood test. Hyperbilirubinemia is revealed with a predominance of indirect bilirubin. The level of total bilirubin does not exceed 200–220 $\mu\text{mol/l}$.
2. Determination of T3, T4, TSH in the blood.

4.2.3. Neonatal hepatitis

Etiopathogenesis. Hepatitis of newborns, as a rule, has an infectious genesis.

Among them are:

1. Congenital neonatal giant cell hepatitis with intrahepatic cholestasis.
2. Postnatal hepatitis caused by intrauterine infections (CMV, listeriosis, toxoplasmosis, rubella virus, Coxsackie, herpes, HAV, HBV, HCV, etc.).
3. Toxic-septic liver damage in sepsis and other infections.

Among neonatal hepatitis with an established cause, hepatitis B, which has a vertical transmission route, occupies the first place. Transmission reaches 70 % of mothers seropositive for HBsAg and HBeAg. Most infected neonates become asymptomatic carriers. Children born to HBeAg-negative mothers have a high risk of developing hepatitis during the first 12 weeks of life as a result of mother-to-child transmission of the pre-mutant virus. It is possible both the absence of the disease and the development of mild and severe forms of hepatitis.

Carriage and hepatitis can be prevented if all children born to carrier mothers are vaccinated.

Hepatitis A is extremely rare in newborns. For hepatitis C, the transplacental route of transmission is not typical.

Clinic. Depends on the duration of exposure to the virus and can occur in 2 variants – subacute (most often) and acute (manifest). Jaundice can be observed from birth or appear in the first 2 to 3 weeks of life, lasts from 2–3 weeks to 2–3 months. The stool becomes weakly colored up to acholic (the severity of acholia indicates the severity of the disease). Urine has a dark color (with the appearance of conjugated bilirubin) due to the high content of bile pigments (urobilin) in it. Characterized by an increase in the liver, its dense consistency, splenomegaly may not be. There is a decrease in appetite, regurgitation, vomiting, bloating, as well as neurological

symptoms (decreased reflexes, hypotension, convulsions, meningeal signs may occur). The hemorrhagic syndrome can join. In some patients, the clinical picture may be dominated by signs of cholestasis, hepatocyte cytolysis, and acute liver failure. With intrauterine infections, sepsis, the symptoms of the underlying disease come to the fore.

Variants of clinical manifestations of hepatitis B in newborns:

- asymptomatic course with laboratory signs of chronic liver damage and persistent positive reactions to HBsAg;
- asymptomatic course or development of mild forms of hepatitis with positive reactions to HBsAg, followed by recovery and disappearance of antigenemia;
- development of severe acute hepatitis with liver necrosis, positive reactions to HBsAg.

Laboratory diagnostics:

1. Biochemical blood test. When determining total bilirubin and bilirubin fractions in the first days of the disease, indirect bilirubin predominates in the analysis, then the proportion of direct bilirubin increases. The activity of aminotransferases and other hepatospecific enzymes is increased. alkaline phosphatase and urokinase levels are also elevated in cholestasis.

2. Prothrombin index – decreases.

3. Determination of the level of alpha-feto-protein. Its content increases in congenital hepatitis.

4. Determination of hepatitis markers (HBsAg, etc.).

5. Research on intrauterine infections. It is carried out by enzyme immunoassay with the determination of specific immunoglobulins.

6. Liver biopsy. With toxic hepatitis, sepsis, signs of cholestasis, focal necrosis of hepatocytes, and areas of fibrosis are revealed.

5. OBSTRUCTIVE (MECHANICAL) JAUNDICES (HEREDITARY AND ACQUIRED)

Cholestasis is a decrease in the flow of bile into the duodenum due to a pathological process in any area from the hepatocyte to the nipple of Vater. Clinically, cholestasis is associated with light-colored stools and dark urine. Cholestasis is the result of structural and functional damage to the hepatobiliary system and can often be a sign of severe and progressive disease.

In newborns with cholestasis, it is necessary to tune in to a broad differential diagnosis, since viral infections, metabolic disorders, and toxic strokes can also be the cause of cholestasis. Fortunately, cholestasis in newborns in most cases is initially accompanied by normal synthetic liver function.

The clinical manifestation of cholestasis is due to the accumulation of normal excreted bile substances: bilirubin, bile acids, cholesterol. Accumulation of direct bilirubin leads to jaundice and dark urine, bile acids cause itching, cholesterol-hypercholesterolemia, and xanthomas.

Children with extremely low body weight have a significantly higher risk of cholestasis. This is due to the immaturity of the biliary excretory system, a high risk of sepsis due to a low immune response, the likelihood of necrotizing enterocolitis, short bowel syndrome, and prolonged parenteral nutrition.

Jaundice is considered prolonged if hyperbilirubinemia persists for more than 6 weeks.

The total number of causes that can lead to the development of cholestasis in newborns, according to various authors, reaches 35–40.

5.1. Malformations of the biliary tract

Frequency: 6–8 % of all congenital anomalies. In a population of 1:10,000 – 20,000 newborns.

Allocate intrahepatic and extrahepatic atresia of the biliary tract.

Etiopathogenesis. Most of the atresia and hypoplasia of the biliary tract is the result of hepatitis (neonatal hepatitis with an established cause – in 45,5 %, idiopathic neonatal hepatitis – in 19,7 %). Worldwide, biliary atresia is the leading cause of chronic liver failure. With intrahepatic atresia and hypoplasia, giant cells (giant cell hepatitis) are found in the liver with

areas of fibrosis and sclerosis around them. Extrahepatic atresia is most commonly caused by reovirus type 3. Violation of the outflow of bile leads to the penetration of its components (including direct bilirubin) into the blood. Progressive dystrophic changes in hepatocytes lead to their necrosis. In conditions of cholestasis, an inflammatory process occurs in the biliary tract – cholangitis. Vitamin K deficiency develops

Clinic. Icteric syndrome in the first days of life may be due to hyperbilirubinemia with a predominance of indirect bilirubin, but later the proportion of direct bilirubin increases and the skin becomes greenish in color. Appears acholic stool, dark urine. The liver is enlarged in size, dense consistency. There are signs of portal hypertension (dilation of the veins of the anterior abdominal wall and others). After 1–2 weeks from the appearance of an acholic stool, hemorrhagic manifestations may develop (due to a deficiency of vitamin K-dependent factors). Skin itching in the neonatal period is not typical. The general condition of the child can be satisfactory within 2–3 months of life.

It is difficult to clinically differentiate extrahepatic and intrahepatic atresia of the biliary tract, but it is important to establish a diagnosis of extrahepatic atresia before 1,5–2 months (surgical treatment in these cases can be successful, otherwise liver cirrhosis develops). Currently, surgical treatment is carried out both for atresia of the distal and proximal sections of the external bile ducts.

In the absence of timely treatment, a fatal outcome occurs within two years, the average life expectancy is eight months. Portoenterostomy according to Kasai in 25–35 % of patients can prolong life up to 10 years or more, followed by liver transplantation. Biliary atresia is by far the most important indication for liver transplantation.

Laboratory diagnostics:

1. General blood test. Increasing anemia and thrombocytopenia are revealed.

2. Biochemical blood test. The total protein is reduced, the level of albumin is reduced, the content of direct bilirubin is increased, the activity of alkaline phosphatase is increased.

3. Determination of the level of alpha-fetoprotein. Its content increases in congenital hepatitis.

4. Coprogram – steatorrhea.

5. Ultrasound of the liver.

6. X-ray examination (possible if the level of bilirubin is not higher than 170 $\mu\text{mol/l}$).

5.2. Bile thickening syndrome

Genesis – blockage of the bile ducts (both extrahepatic and intrahepatic) with mucous plugs. May complicate any jaundice with overproduction of bilirubin.

Clinic. The bile thickening syndrome usually appears on 5–12 days of life and is manifested by increased jaundice, a greenish coloration of the skin, and discolored stools. Usually disappears in 1–4 days under the influence of therapy, or spontaneously.

5.3. Biliary hypoplasia

There are many variants of cholestasis that are associated with intrahepatic biliary hypoplasia, such as the absence or reduction of part of the intralobular bile ducts or capillaries. The size of the portal vein and hepatic artery in these children correspond to the norm. The most studied condition is Alagille syndrome, described in 1975.

Alagille syndrome.

Alagille syndrome is inherited in an autosomal dominant manner with a frequency of 1:100,000 live births. It is characterized by multisystem disorders with damage to the heart, the development of facial, renal, visual and skeletal anomalies. The prognosis depends on the severity of liver and heart damage. In 50 % of children, normalization of liver function occurs as they grow older.

5.4. Cysts

Perhaps the presence of 3 types of cysts: extrahepatic (most), intrahepatic and mixed. All patients with cysts have prolonged jaundice in the neonatal period. Mortality among patients with multiple cysts is much higher due to the development of secondary complications in the form of cholangitis.

5.5. Congenital biliary dilatation

Diagnosis of congenital biliary dilatation is possible even in the antenatal period. Surgical treatment carried out in the first 2 months of life can provide a favorable prognosis.

Other rare causes of cholestasis in newborns include:

1. Syndrome of lymphedema and cholestasis – Aa genas-syndrome-T.
2. Gaucher disease.
3. Diabetes mellitus.
4. Syndrome Dubin – Johnson.
5. Hypothyroidism.
6. Congenital hepatic fibrosis.
7. Sclerosing cholangitis.
8. Diaphragmatic hernia.
9. Juvenile xanthogranuloma.
10. Autoimmune enteropathy.
11. Galactosemia.
12. Syndrome Zellweger.
13. Niemann – Pick disease, type C (NPCs).
14. Anomalies in the structure of bile acids.
15. Necrotizing enterocolitis.

5.6. Transient neonatal cholestasis

The development of transient neonatal cholestasis is based on acute and chronic perinatal liver hypoxia. The development of cholestasis is noted on average by 7 days of life, it can last up to 3,5 months. Hepatosplenomegaly sometimes persists for up to a year. The risk of developing neonatal cholestasis is very high in newborns born before 35 weeks of gestation with antenatal malnutrition. Among full-term newborns with normal weight, the frequency of transient cholestasis does not exceed 8,5 %.

5.7. Familial intrahepatic cholestasis

Familial intrahepatic cholestasis was originally described as Byler's disease. Currently considered as 3 different conditions leading to impaired transport of bile salts and associated with defects in chromosomes 2 and 18. There are 3 types of FIC. In the first and second types (FIC1 and FIC2), there is a low level of serum g-glutamyl transpeptidase, in the third (FIC3) – a high level of g-glutamyl transferase. The development of type 2 is due to a mutation in the BSEP (bile salt export pump) gene, which encodes the pumping transport of bile salts.

5.8. Symptomatic cholestasis

A. Alpha-1-antitrypsin deficiency

Type of inheritance: autosomal recessive.

Clinic. Similar to the picture of cholestatic hepatitis: jaundice appears from the first days of life, due to hyperbilirubinemia with a predominance of direct bilirubin, characterized by a protracted course. The stool is acholic, bile pigments appear in the urine. The liver is enlarged in size, with an unfavorable course of the disease, an outcome in cirrhosis is possible, with mild forms, recovery is possible by the second half of the year of life.

Laboratory diagnostics:

1. Biochemical blood test – determination of total bilirubin and bilirubin fractions, protein electrophoresis – absence or sharp decrease of less than 1 % of alpha-1-globulins
2. Determination of antitryptic activity of serum and serum concentration of alpha-1-antitrypsin by immunodiffusion-reduced.
3. Histology of the liver – portal fibrosis, PAS-positive lumps in the cytoplasm of hepatocytes.

B. Cystic fibrosis

The frequency of cystic fibrosis: 1:2,500 newborns in Europe. The liver in this disease is affected in 20–40 % of cases.

Clinic. Jaundice in cystic fibrosis is associated with cholestasis due to blockage of the bile ducts with thick mucus. Destructive changes in the liver begin early, sometimes already in the prenatal period, later cirrhosis may develop.

Laboratory diagnostics:

1. Biochemical blood test – mixed type hyperbilirubinemia.
2. Coprogram – steatorrhea.
3. Determination of sodium and chlorine in sweat increased to 60 mmol/l.
4. Screening test of newborns – increased immunoreactive trypsin in the blood.
5. Analysis of feces for trypsin and chymotrypsin – sharply reduced.
6. Liver biopsy – characteristic eosinophilic plugs and hyaline deposits in the interlobular bile ducts and steatorosis.

!!! Jaundice with direct hyperbilirubinemia (no attachment to the timing of occurrence more often – as a consequence of cholestasis) **always require clarification of the diagnosis!!!** (Application No. 5)

6. LIVER INSUFFICIENCY IN NEWBORN

Liver failure is rare in newborns and may be due to various causes. It must be remembered that acute and chronic liver failure, regardless of the cause that caused them, are characterized by the obligatory presence of three syndromes: jaundice, encephalopathy and coagulopathy. The severity of each of the syndromes may be different.

Acute liver failure

The clinical picture of acute liver failure can develop very quickly, within a day, but can be prolonged up to 10 weeks if caused by metabolic liver disease. The intensity of jaundice and the severity of encephalopathy vary at different stages, but all patients have coagulopathy. Hepatic encephalopathy is difficult to diagnose in newborns, and early signs include vomiting and decreased appetite.

The main causes of acute liver failure in newborns (Kelly O., 2002):

- Hepatitis B;
- Neonatal hemochromatosis;
- Tyrosinemia type I;
- Mitochondrial disorders;
- Familial hemophagocytic syndrome;
- Sepsis.

Indications for liver transplantation in children with acute liver failure (Kelly O., 2002)

Indications for urgent liver transplantation are:

- prothrombin time >60 s;
- decrease in the level of transaminases;
- increase in blood bilirubin >300 mmol/l;
- reduction in the size of the liver;
- pH < 7,3;
- hypoglycemia <4 mmol/l;
- hepatic coma of 2 or 3 degrees.

A contraindication for liver transplantation is multisystem diseases such as mitochondrial disorders, as well as severe cerebral changes detected during brain imaging using computed tomography or magnetic resonance imaging.

7. JAUNDICE OF MIXED GENESIS

Jaundice of healthy newborns (physiological)

Physiological jaundice is a diagnosis of exclusion of pathological jaundices. An important task of a pediatrician during the period of monitoring the health of a newborn child is to distinguish between physiological features and pathological disorders of bilirubin metabolism.

Physiological jaundice is understood as icteric coloration of the skin, which is observed in most newborns in the first days of life. The pathogenesis of physiological jaundice is due to the accumulation of indirect bilirubin in the blood as a result of the temporary immaturity of the glucuronyl transferase system of the liver. In premature babies, the restoration of the glucuronyl transferase system occurs later, jaundice has a prolonged course, sometimes up to 2–3 months.

Physiological jaundice is observed in the vast majority of full-term and premature newborns (in 60 and 80 %, respectively).

Clinical Criteria:

- 1) appears 24–36 hours after birth;
- 2) increases during the first 3–4 days of life;
- 3) the rise in the level of bilirubin does not reach a critical level that can cause kernicterus;
- 4) begins to fade from the end of the first week of life;
- 5) disappears in the second or third week of life;
- 6) skin has an orange tint;
- 7) the general condition of the child is satisfactory;
- 8) not enlarged liver and spleen;
- 9) normal color of feces and urine;
- 10) disappears on the 2–3rd week of life (traditionally in full-term – by the 10th days, in premature babies – by the 14th day).

Laboratory Criteria:

- 1) Concentration of bilirubin in umbilical cord blood (moment of birth) – less than 51 μmol ;
- 2) the concentration of hemoglobin in cord blood is normal;
- 3) hourly increase in bilirubin in the first day of life is less than 5,1 $\mu\text{mol/l/hour}$;
- 4) maximum concentration of total bilirubin on the 3rd – 4th day in peripheral or venous blood: $\leq 256 \mu\text{mol/l}$ in term, $\leq 171 \mu\text{mol/l}$ in preterm infants;

- 5) total blood bilirubin increases due to the indirect fraction;
- 6) the relative proportion of the direct fraction is less than 20 %;
- 7) normal values of hemoglobin, erythrocytes and reticulocytes in clinical blood tests;
- 8) hourly increase in NB in the first day of life does not exceed 3,4 $\mu\text{mol/l}$, daily – 85 $\mu\text{mol/l}$;
- 9) the maximum level of total bilirubin in venous blood is not exceeds 255 $\mu\text{mol/l}$, NB – 220 $\mu\text{mol/l}$;
- 10) the peak of the rise in bilirubin falls on the 4–5th day in full-term babies, on the 7–8th day of life in premature newborns;
- 11) the content of direct bilirubin does not exceed 10–15 % of the total the amount of bilirubin (up to 25 $\mu\text{mol/l}$);

With physiological jaundice, there is no need for extensive examination and treatment.

The increase in bilirubin in the first day of life is due to the following factors:

- 1) a large amount in the bone marrow, liver, spleen erythrocyte precursors that do not have time to mature;
- 2) a shorter period of existence of circulating erythrocytes (in average 70–80 days);
- 3) a large volume of circulating red blood cells.

Physiological jaundice goes through two temporary phases. The first covers 5 days of life from the moment of birth and is characterized by a relatively rapid increase in the level of free (unconjugated) bilirubin to an average peak value of approximately 5 mg % (85 $\mu\text{mol/l}$) on the third day of life, and a sharp decrease in the concentration of bilirubin by the 5th day. The second phase is characterized by a slow decrease in indirect bilirubin, which reaches the normal level characteristic of adults by the 11–14th days of life.

Any deviation from the "normal course" of physiological jaundice should be considered as signs of pathology.

8. EXAMINATION OF NEWBORN WITH JAUNDICE

When examining a newborn with jaundice, the following questions should be answered:

1. When did jaundice appear?
2. What is the general condition of the child?
3. What is the nature of jaundice (hue)?
4. How do the sizes of the liver and spleen change?
5. What is the color of urine and feces?
6. Are there any hemorrhagic manifestations?

!!! It is necessary to reflect in the outpatient card:

- the dynamics of the child's well-being;
- type of feeding;
- color of the skin;
- the presence and change in the nature of regurgitation;
- size of the liver and spleen;
- color of urine and stool.

8.1 Principles for the management of children with hyperbilirubinemia

- Clinical and anamnestic, clinical and laboratory screening.
- Identification of the mechanism and causes of hyperbilirubinemia.
- Creating optimal conditions for child care.
- Treatment of the underlying disease.
- Phototherapy – with indirect hyperbilirubinemia (observing safety rules, taking into account side effects).
 - Inspection is carried out, completely undressing the child, in daylight, exercising light pressure on the skin (Cramer scale).
 - The Cramer scale is subjective! It can be used to identify indications for a biochemical blood test in the absence of devices for percutaneous determination of bilirubin.

All methods for determining the level of bilirubin can be divided into two groups:

1. Invasive methods – determination of the concentration of bilirubin in biological fluids by biochemical methods.
2. Non-invasive methods – determination of the concentration of bilirubin in the blood by percutaneous – transcutaneous method.

8.2. Using a biochemical method for determining the level of bilirubin in blood serum

The most common is the biochemical method for determining the level of bilirubin in the blood serum (the Yendrashik method and its modifications). When using the routine method, at least 0.7 ml of serum is required, the micromethod allows you to limit yourself to 0.4 ml of serum.

The advantage of the biochemical method:

- the possibility of separate determination of direct and indirect bilirubin.

Disadvantages of the method:

- the need to use large volumes of blood for research;
- the complexity of technical blood sampling from a vein, the possibility of hemolysis, especially in children with low weight, in the presence of a serious illness;
- the impossibility in some cases of multiple examinations of the child during the day, which is necessary to determine the hourly intake of bilirubin;
- incompatibility of results when using different methods for determining bilirubin in blood serum;
- the need for frequent calibration and independent laboratory control;
- the need for special reagents in the laboratory;
- obligatory availability of special personnel in the laboratory, which requires large material costs.

8.3. Transcutaneous method for determining the level of bilirubin

Advantages of the method:

- availability, ease of use, portability of the device;
- the ability to conduct multiple measurements during the day by any caring staff (nurse, parents);
- non-invasiveness and painlessness for the child, regardless of his gestational age, body weight and day of life;
- the ability to control the course of jaundice, to objectively determine its increase and decrease;
- the ability to use the device in outpatient and home conditions to control the course of jaundice;

- the ability to determine the individual effectiveness of phototherapy.

Disadvantages of the method:

- transcutaneous bilirubinometry allows you to measure the transcutaneous bilirubin index (TBI), i.e. the level of bilirubin in the dermis, and not in the blood serum, therefore, the TBI value conveys only the dynamics of the process;
- the device requires a fairly frequent change of batteries or recharging of the battery device;
- the device is not suitable for use in children with severe forms of hemolytic disease, when hemolysis and the increase in free bilirubin in the blood significantly outpace its penetration into the dermis.

Transcutaneous measurement of bilirubin in newborns is more objective than the Cramer scale, a screening method:

- allocate groups of children for biochemical examination of blood (more than 250 $\mu\text{mol/l}$ over the age of 72 hours in full-term and late preterm infants);
- Bilitest is used for 5 days (the critical period for the growth of neonatal jaundice), 7 and 10 days of life;
- ease of use during patronage, at the reception in clinics;
- the measurement in the forehead area is as comparable as possible with a biochemical blood test;
- method – does not show the fraction of bilirubin; error $\pm 15\%$; do not use in children under 35 weeks.

For timely and reasonable diagnosis of the level of hyperbilirubinemia in newborns, at all levels of care, there should be devices and methods for the “three levels of diagnosis”:

1. The use of the transcutaneous method as a screening method to identify a group of children who need to control the level of bilirubin in the serum and its increase, as well as control jaundice in case of a protracted course.

2. Dynamic monitoring of children with moderate and severe forms of hyperbilirubinemia should be carried out using direct spectrophotometry due to the accuracy, ease of execution of the method, low trauma for the child, and the ability to conduct multiple measurements.

3. The study of the level of bilirubin by a biochemical method should be carried out if it is necessary to determine the fractions of bilirubin in HDN, suspected hepatitis, "post-hepatic" violation of bilirubin metabolism due to malformations of the biliary system, with cholestasis, as well as with suspicion of genetically determined jaundice (Crigler – Najjar type).

8.4. Clinical significance of the determination of γ -glutamyl transpeptidase

γ -glutamyl transpeptidase (GGT) is a microsomal enzyme widely distributed in human tissues, involved in the secretory process and absorption, especially in the bile ducts. The level of GGT in the blood serum increases in diseases of the liver associated with damage to the biliary system, such as extrahepatic biliary atresia, sclerosing cholangitis, progressive familial intrahepatic cholestasis type 3: Types 1 and 2 PS have a normal or low level of GGT activity.

The determination of GGT is used to detect cholestasis caused by parenteral nutrition and to evaluate therapy with ursodeoxycholic acid. The level of GGT fluctuations is associated with age. In newborns with normal thermoregulation, GGT activity is 6–7 times higher than in adults. By 5–7 months of life, GGT activity decreases to the "adult level".

8.5. Instrumental methods of examination of newborns with jaundice

The methods of choice are ultrasound, hepatoscintigraphy with mebrofenin, magnetic resonance cholangiography.

Other instrumental research methods

1. Duodenal test is performed to diagnose biliary atresia, in which a nasoduodenal probe is inserted to the distal duodenum and fluid is collected within 24 hours (Larrosa-Haro et al.). The duodenal test is considered positive if a bile-colored liquid appears, in which case further research is stopped and the probe is removed. The absence of bile within 24 hours indicates a negative duodenal test and the presence of biliary atresia.

2. Laparoscopy especially important in cases where diagnosis is difficult in children with biliary atresia and neonatal hepatitis. A dark green color of the liver and an enlarged gallbladder confirm extrahepatic biliary obstruction.

3. Needle liver biopsy is performed in children with unclear diagnosis and suspected intrahepatic origin of jaundice. Severe jaundice is not a contraindication for liver biopsy, but its presence increases the risk of biopsy complications.

9. TREATMENT OF HYPERBILIRUBINAMIA

Indications for hospitalization for persistent hyperbilirubinemia:

- 1) worsening condition (manifestations of bilirubin intoxication – loss of muscle tone, sluggish sucking, decreased appetite, reflexes, monotonous cry, regurgitation, vomiting);
- 2) serum bilirubin more than 200 $\mu\text{mol/l}$ without a tendency to decrease or with its increase (exceeding the 3rd zone on the Cramer scale) after 7–10 days of life;
- 3) fraction of direct bilirubin more than 20% of total serum bilirubin;
- 4) enlargement of the liver and/or spleen;
- 5) the presence of dark urine and discolored stools;
- 6) manifestations of hemorrhagic syndrome (bleeding, rash).

I. Operational:

- a) blood transfusion;
- b) plasmapheresis;
- c) hemosorption.

Laboratory tests:

1. Level of bilirubin: in cord blood more than 170 $\mu\text{mol/l}$; on the 1st day – more than 170 $\mu\text{mol/l}$; on the 2nd day – more than 256 $\mu\text{mol/l}$; on the 3rd day – more than 340 $\mu\text{mol/l}$.
2. Hourly increase in bilirubin more than 7–8 $\mu\text{mol/l}$.
3. Hemoglobin level less than 110 g/l.

Clinical:

1. Presence of signs of severe HDN at birth in children born of mothers with proven sensitization (positive Coombs test, severe HDN with OZK in previous children).

2. The appearance of signs of bilirubin intoxication in a newborn.

Blood selection for replacement blood transfusion surgery:

1. The replacement blood transfusion surgery operation is carried out in 2 or 3 times the volume of circulating blood, which in newborns is 85–90 ml and, accordingly, is 170–250 ml/kg.

2. For the operation, "fresh" blood is used, the harvesting period is not more than 3 days.

The components of transfused blood depend on the type of conflict:

1. In case of Rh-incompatibility – whole Rh-negative blood is transfused, one-group with the child's blood.

2. In case of ABO-incompatibility – erythrocyte mass of O (I) group (washed erythrocytes) of blood, Rh belonging to the child and plasma of AB (IV) blood groups in a ratio of 2:1.

3. In case of a double conflict, the erythrocyte mass of the O (I) group, Rh-negative and AB (IV) plasma are transfused in a ratio of 2:1.

Possible complications of the exchange blood transfusion operation:

1. Heart failure (with the rapid introduction of a large amount blood due to hypervolemia, volume overload);

2. Cardiac arrhythmias and cardiac arrest due to hyperkalemia, hypocalcemia or excess citrates;

3. Infection;

4. Air embolism (with a small diameter of the catheter due to negative pressure in the umbilical vein);

5. Perforation of the umbilical vein and intestines with a catheter;

6. Thrombosis of the portal vein (due to catheter injury and increased viscosity blood);

7. Portal hypertension;

8. Anaphylactic shock;

9. Hypothermia;

10. Disseminated intravascular coagulation syndrome.

II. Conservative treatment of jaundice:

1. Infusion therapy.

It is carried out in order to detoxify, improve the processes of conjugation and excretion of bilirubin.

1. Solutions used: crystalloids – 5 to 7.5–10 % glucose solutions; colloids – 5–10 % albumin solution (10–15 ml/kg). Contraindicated in critical numbers of bilirubin.

2. The volume of fluid for infusion therapy is usually from 30 to 70 ml/kg of the child's body weight.

3. The rate of intravenous drip of liquid – 3–5 drops per minute (10 ml/hour).

2. Phototherapy is the most effective and safe method of conservative treatment of jaundice.

1. The essence of phototherapy: under the action of light with a wavelength of 460 nm, the toxic isomer of bilirubin Z-Z is converted in the skin into a non-toxic isomer Y-Y, which is water-soluble and excreted by the kidneys.

2. Blue (daylight) and blue and green light lamps are used.

3. The distance from the lamp to the child is 45–50 cm.

4. Indications for the beginning of phototherapy: the level of bilirubin in full-term newborns is more than 205 $\mu\text{mol/l}$; in premature babies – 170 $\mu\text{mol/l}$.

5. Treatment is carried out continuously (24 hours a day) and intermittent methods (2 hours after 2 hours, 4 hours after 2 hours). Phototherapy for less than 12 hours per day is considered ineffective.

6. For the duration of the session, the child is placed naked in an incubator. The eyes and gonads are closed.

7. Heating dose 72–90 hours.

8. Phototherapy is canceled when the level of bilirubin reaches physiological figures for a given age of the child.

Side effects of phototherapy:

1. Loss of water. To prevent it, children should additionally receive liquid in a volume of 20–25 ml/kg;

2. Green stool (photo derivatives of bilirubin are removed);

3. Syndrome "bronze child". Seen in children with high numbers direct bilirubin;

4. Transient skin rash;

5. Transient deficiency of vitamin B2;

6. Overheating;

7. Tendency to thrombocytopenia, hemolysis.

Contraindications to phototherapy:

1. Severe anemia;

2. Sepsis;

3. Mechanical jaundice;

4. Hemorrhagic syndrome.

Not prescribed for indirect hyperbilirubinemia:

- Enzymes;

- Vitamins;

- Smecta;

- Viferon;

- Hepatoprotectors;

- Ursafalk is prescribed for cholestasis (10–20 mg/kg/day).

3. Medical treatment.

1. Activation of the liver conjugation system (phenobarbital, zixorin, 5–10–15 mg/kg/day).

2. Drugs that adsorb bilirubin in the intestine (cholestyramine 1,5 g/kg/day; agar-agar 0,3 g/kg/day; carbolene 0,15–0,25 g/kg/day).

3. Cholagogue preparations (allohol, 12,5 % solution of magnesium sulphate inside; 2 % and 6 % in the form of electrophoresis on the liver area).

4. Cell membrane stabilizers (vitamins E, A; ATP) .

5. Hepatoprotectors (Essentiale, Riboxin).

RED FLAGS

1. Loss of body weight and gain per month less than 500 g.
2. Unusually "big belly".
3. Frequent, profuse regurgitation, which appeared at 3–4 weeks, especially accompanied by weight loss.
4. Unusual skin color or shade on the background of jaundice.
5. A change in the child's consciousness that has come on acutely or is growing.
6. Drowsiness, lethargy of the child.
7. Prematurity or immaturity.
8. The appearance of jaundice in a child on artificial feeding.
9. The appearance of jaundice after several weeks of its absence.
10. The predominance of the direct fraction of bilirubin in the biochemical analysis of blood or an equal ratio of direct and indirect fractions.
11. Any diseases that are identified during the examination.
12. Anemia, especially with a high level of reticulocytes.

ISSUES OF VACCINATION OF CHILDREN WITH HYPERBILIRUBINEMIA

Jaundice is an indication for a temporary medical exemption (time for differential diagnosis)!

With the extinction of jaundice, satisfactory condition, total bilirubin 40–60 $\mu\text{mol/l}$ in a biochemical blood test, vaccination is indicated.

PREVENTION OF HDN

1. Family planning.
2. Introduction to primiparous and primiparous (not sensitized) women who gave birth to Rh-positive children, anti-Rh-globulin in the first 3 days after delivery.
3. Replanting a "skin flap" of a husband, a pregnant woman.
4. Introduction of a lymph suspension of a husband, a pregnant woman.

5. Ultrasound monitoring of the fetus and determination of antibody titer in women who are at risk for the development of HDN of the fetus and newborns for timely delivery (in the period of 36–37 weeks). Pregnancy should not be allowed to continue.

REHABILITATION OF CHILDREN AFTER HEMOLITIC DISEASE OF THE NEWBORN

Children who have had HDN need dispensary observation and rehabilitation therapy in the office of a pediatrician, family doctor with the participation of a neuropathologist, otolaryngologist, ophthalmologist, and speech therapist.

To carry out rehabilitation measures, the doctor needs to know:

- obstetric history (the course of pregnancy, childbirth, the presence of extragenital pathology, the outcome of previous pregnancies);
- severity of HDN, treatment performed in the maternity ward;
- indicators of the general blood test, the concentration of bilirubin, its maximum numbers, the degree of anemia at birth and discharge.

Based on these data, the pediatrician, together with a neuropathologist, an otolaryngologist, and, if necessary, with other specialists, draws up a plan for dispensary observation, examination, and rehabilitation therapy.

Rehabilitation plan.

a) examination:

- complete blood count after discharge and in dynamics after 7–10 days with the determination of the level of reticulocytes once a month;
- the concentration of bilirubin in the blood in dynamics 1 time per week;
- general urinalysis, bile pigments;

b) consultations of a neuropathologist, otolaryngologist, ophthalmologist in the first 2–3 weeks of life.

Rehabilitation measures are determined by the complications that have developed in children who have had HDN: CNS damage, the presence of anemia or bile thickening syndrome.

Early anemia develops in almost all children who have had HDN. They are hyporegenerative, transient in nature.

Treatment of anemia I stage – proper care, breastfeeding, maximum exposure to fresh air, a complex of vitamins: C – 0,05 g, B1 – 0,001 g, B2 – 0,002 g 1 time per day for 2–3 weeks.

Treatment of anemia II stage: in addition – vitamin B6 (10–12 injections) and vitamin B12, 50 mcg every other day (10 injections).

Treatment of anemia III stage: carried out in a hospital. The transfusion of erythrocyte mass is shown.

Bile thickening syndrome. Treatment: choleretic – 10–12,5 % solution of magnesium sulfate, 10 ml, preferably through a tube, or holosas (3–5 drops), sorbitol 0,5 g (dissolved in water, 5–10 ml per day); duodenal sounding, heat on the liver area; magnesium sulfate electrophoresis, activated carbon – 0,3 g for the adsorption of bilirubin in the intestine. The duration of treatment is 3–5 days.

Rehabilitation measures in children with CNS lesions depend on the severity of the pathology. Treatment and rehabilitation are carried out in specialized neuropsychiatric departments by a psychoneurologist, physiotherapist with the participation of a pediatrician, otolaryngologist, ophthalmologist, orthopedist.

CONCLUSION

Purposeful elucidation of the causes leading to the development of jaundice in newborns, a comprehensive analysis of the clinical status, as well as a detailed assessment of background conditions allow timely diagnosis and selection of adequate tactics for managing the child, which not only improves the prognosis of the disease, but also improves the quality of his life in the future

TEST SELF-CONTROL OF KNOWLEDGE

Choose one correct answer.

1. ABSOLUTE CONTRAINDICATIONS TO BREASTFEEDING ARE ALL EXCEPT ONE:

- galactosemia
- phenylketonuria
- disease "urine with the smell of maple syrup"
- + hemolytic disease of the newborn according to the Rh factor, starting from the 6th day from birth

2. DEVELOPMENT OF HEMOLYTIC DISEASE OF THE NEWBORN BY ABO ASSOCIATED WITH:

- the presence of natural alpha and beta hemagglutinins in the mother
- the presence of natural alpha and beta hemagglutinins in the fetus
- + maternal production of immune hemolysins (anti-A or anti-B) against erythrocyte antigens (A or B) of the fetus
- development in the fetus of immune hemolysins (anti-A or anti-B) against maternal erythrocyte antigens (A or B)

3. WHAT IS THE DECLINE OF HEMOGLOBIN AT THE 1st MONTH OF LIFE IN A HEALTHY TERM NEWBORN CHILD?

- + with natural erythrocyte hemolysis
- with inhibition of bone marrow function
- with activation of the reticulo-histiocytic system
- all of the above factors

4. WHAT COMPLICATION IS THE MOST SEVERE IN ICTERIC FORM OF HEMOLYTIC DISEASE OF THE NEWBORN

- anemia
- liver damage
- + CNS damage
- heart failure

5. WHAT IS THE MOST COMMON CAUSE OF ANEMIA AT BIRTH?

- + blood loss or hemolysis
- hereditary microspherocytosis
- deficiency of erythrocyte enzymes
- hereditary hypoplastic anemia

6. WHICH CONSERVATIVE THERAPY IS THE MOST EFFECTIVE IN THE TREATMENT OF FREE HYPERBILIRUBINEMIA IN NEWBORN CHILDREN?

- phototherapy

- treatment with phenobarbital
- infusion therapy
- + combination of the listed methods

7. UNTIL WHAT AGE IS HEMOGLOBIN DECREASED IN HEMOLYTIC DISEASE OF THE NEWBORN?

- up to 2 weeks of life
- up to 1 month
- up to 1.5 months
- + up to 2 months

8. WHAT IS THE CLINIC DIFFERENCE OF RESPIRATORY INSUFFICIENCY IN NUCLEAR JAUNDICE FROM PNEUMONIA?

- nothing different
- the presence of moist rales in the lungs
- severe shortness of breath
- + sharp depression of the respiratory center (bradypnea)

9. WHAT FACTORS CONTRIBUTE TO THE DEVELOPMENT OF BILIRUBIN ENCEPHALOPATHY?

- hypoxia
- acidosis
- hypoglycemia
- + all listed

10. WHEN SHOULD BILIRUBIN ENCEPHALOPATHY PROPHYLAXIS START IN CONJUGATIONAL JAUNDICE OF PREMATURE HIGH-RISK CHILDREN?

- + from the first day of life
- from the second day of life
- at the height of jaundice
- at any time when signs of bilirubin intoxication appear

11. WHAT TYPE OF ANEMIA IS THE MOST COMMON IN PREMATURE CHILDREN WITH A BODY WEIGHT LESS THAN 1500 G DURING THE FIRST THREE WEEKS OF LIFE?

- iron deficiency
- + vitamin E
- scarce
- protein deficiency
- vitamin B12 – deficient

12. BY THE EARLY DEVELOPMENT OF IRON DEFICIENCY ANEMIA, PREMATURE CHILDREN ARE MOST RISKED:

- + post–natal severe infections
- with intrauterine malnutrition

- immature for gestational age
- with general edematous syndrome

13. REPLACEMENT HEMOTRANSFUSION TO PREMATURE CHILDREN WITH IRON DEFICIENCY ANEMIA IS INDICATED AT THE LEVEL OF HEMOGLOBIN:

- 150 g/l
- 100–90 g/l
- + 70 g/l

14. PHOTOTHERAPY IN PREMATURE CHILDREN MAY BE COMPLICATED:

- + the appearance of loose stools with an admixture of greenery
- bile thickening syndrome
- development of hemolytic anemia
- attachment of infection

15. FROM THE LISTED VIRAL INFECTIONS, THE DEVELOPMENT OF JAUNDICE IS NOT CHARACTERISTIC FOR:

- infectious mononucleosis
- cytomegalovirus infection
- + hemorrhagic fever with renal syndrome
- herpetic infection

16. FROM THE LISTED BACTERIAL INFECTIONS, THE DEVELOPMENT OF JAUNDICE CAN BE OBSERVED WITH:

- sepsis
- leptospirosis
- pseudotuberculosis
- syphilis
- + meningococcal infection

17. UNCONJUGED BILIRUBIN IS A COMPLEX BILIRUBIN C:

- fatty acids – glucose
- + albumin
- transferrin
- all of the above

18. CONJUGED BILIRUBIN IS A BILIRUBIN COMPLEX WITH:

- amino acids
- + glucuronic acid
- glucose – vitamins
- salts of fatty acids

19. PHYSIOLOGICAL NEWBORN JAUNDICE DEVELOPES AS A RESULT OF:

- increased formation of indirect bilirubin due to the shortened lifespan of erythrocytes with fetal hemoglobin

- hypoalbuminemia
- decreased activity of glucuronyltransferase
- increased formation of indirect bilirubin due to shortened lifespan of erythrocytes with fetal hemoglobin and hypoalbuminemia
- + increased formation of indirect bilirubin due to shortened lifespan of erythrocytes with fetal hemoglobin, hypoalbuminemia and decreased activity of glucuronyl transferase

20. JAUNDICE WITH GILBERT SYNDROME IS DECREASED WHEN USING:

- + phenobarbital
- antisecretory drugs
- prokinetics
- essentielle forte
- sulfonamides

21. IN HYPOTHYROIDISM IN NEWBORN PROCESSES OF BILIRUBIN CONJUGATION:

- + slow down
- do not change
- are accelerating

22. THE CAUSE OF HEMOLYTIC DISEASE OF THE NEWBORN IS:

- immaturity of liver glucuronyltransferase
- + isoimmune hemolytic anemia
- hemoglobinopathy
- intrauterine infection
- autoimmune hemolytic anemia

23. WHEN THE BLOOD OF THE MOTHER AND THE FETUS IS INCOMPATIBLE FOR THE RH-FACTOR, THE HEMOLYTIC DISEASE OF THE NEWBORN DEVELOPS MORE OFTEN:

- first pregnancy
- + in repeated pregnancies

24. A MORE SEVERE COURSE OF HEMOLYTIC DISEASE OF THE NEWBORN IS OBSERVED IF THE BLOOD OF THE MOTHER AND THE FETUS IS INCOMPATIBLE FOR:

- + Rh-factor
- blood type

25. HEMOLYTIC DISEASE OF A NEWBORN DURING THE 1st PREGNANCY IS MORE FREQUENTLY CAUSED BY BLOOD INCOMPATIBILITY OF THE MOTHER AND THE FETUS:

- + by ABO system
- according to the Rh-factor

26. JAUNDICE IN HEMOLYTIC DISEASE OF THE NEWBORN APPEARS:

- + up to 48 hours of life
- after 48 hours of life
- after 7 days of life
- after 10 days of life

27. RECOVERY AS AN OUTCOME OF FETAL HEPATITIS:

- + possible
- impossible

28. FORMATION OF ATRESIA OF THE BILE TRACTS AS A RESULT OF TRANSFERRED FETAL HEPATITIS:

- + possible
- impossible

29. MANIFESTATIONS OF HEMOLYTIC DISEASE OF THE NEWBORN ARE:

- + hepatosplenomegaly
- hemorrhagic syndrome
- thrombocytopenia
- + anemia
- dyspeptic syndrome

30. THERAPY OF HEMOLYTIC DISEASE OF THE NEWBORN IS USED:

- hormone therapy
- + intravenous administration of standard immunoglobulin
- + phototherapy
- antibiotic therapy
- + exchange transfusion

31. HYPERBILIRUBINAMIA WITH INCREASED LEVEL OF DIRECT BILIRUBIN IS NOTICED WHEN:

- hemolytic disease of the newborn
- + deficiency of α -1-antitrypsin
- conjugative jaundice due to morpho-functional immaturity
- + atresia of bile ducts
- + fetal hepatitis

32. PHYSIOLOGICAL NEWBORN JAUNDICE IS CHARACTERIZED:

- satisfactory general condition
- normal color of feces and urine
- anemia, enlargement of the liver and spleen
- + satisfactory general condition, normal color of feces and urine

33. JAUNDICE IN GALACTOSEMIA AND CYSTIC FIBROSIS IS CHARACTER:

- conjugative
- mechanical
- hemolytic
- + parenchymal

34. JAUNDICE WITH UNCOMPLICATED HEMOLYTIC DISEASE OF NEWBORN DISAPPEARS:

- by the end of the 1st week of life
- + by the end of the 2nd week of life
- by the end of the 3rd week of life
- by the end of the 1st month of life

35. CRITERIA FOR PHYSIOLOGICAL JAUNDICE IN A NEWBORN BABY IS:

- appearance after 36 hours of life
- for a maximum of 3–4 days of life
- extinction after 10 days of life
- the maximum value of total bilirubin does not exceed 205 $\mu\text{mol/l}$ in full-term children
- + all answers are correct

36. INDICATIONS FOR PRP IN A TERM NEWBORN WITH HDN MAY BE:

- clinical manifestations of edematous
- anemic form of hemolytic disease of the newborn at birth – decrease in hemoglobin in the central blood below 120 g/l (in the peripheral below 140 g/l) in the first 2 days of life
- hourly increase in bilirubin above 6.8 $\mu\text{mol/l}$ per hour in the first 2 days of life
- an increase in the level of indirect bilirubin in the blood serum of term infants above 342 $\mu\text{mol/l}$
- + all answers are correct

37. THE FIRST SYMPTOMS OF BILIRUBIN INTOXICATION IN NEWBORN CHILDREN ARE:

- intense excitement
- + the appearance of symptoms of oppression
- increased muscle tone
- neck stiffness

38. FOR THE DIAGNOSIS OF HEMOLYTIC ANEMIA, THE FOLLOWING IS REQUIRED:

- family history information
- number, shape and size of erythrocytes

- level of reticulocytosis
- osmotic stability of erythrocytes
- + all answers are correct

39. DIRECT COOMBS TEST IS POSITIVE WHEN:

- + hemolytic disease of the newborn by Rh-factor
- HDN according to the ABO system – hemorrhagic disease of the newborn
- thalassemia

40. DIFFERENTIAL DIAGNOSIS IN GALACTOSEMIA SHOULD BE CARRIED OUT WITH:

- intrauterine infections accompanied by jaundice
- sepsis
- hemolytic and non-hemolytic jaundice
- + all listed diseases

41. THE MAIN OBJECTIVE OF THE DISTRICT PEDIATOR IN THE PRESENCE OF JAUNDICE IN A NEWBORN IS:

- appointment of hepatoprotectors
- prescribing choleretic drugs
- + exclusion of the pathological type of jaundice
- appointment of additional drink

42. DEVELOPMENT OF NUCLEAR JAUNDICE IN TERM NEWBORN MAY OCCUR WHEN THE LEVEL OF INDIRECT BILIRUBIN, COMPONENT (MKMOL/L):

- 170–249
- 150–169
- + 340 and more
- 250–300

43. THE MAIN METHOD OF TREATMENT OF JAUNDICE WITH PREDOMINATION THE INDIRECT FRACTION OF BILIRUBIN IN NEWBORN IS:

- + phototherapy
- phenobarbital
- infusion therapy
- hepatoprotector

44. INCREASED ACTIVITY IS CHARACTERISTIC FOR MECHANICAL JAUNDICE:

- + alkaline phosphatase
- AST
- ALT
- aldolases

45. CONJUGATIONAL JAUNDICE APPEARS IN A NEWBORN FOR ____ DAYS OF LIFE:

- 6
- 1
- 5
- + 3

46. WHAT LEVEL OF HEMOGLOBIN IS CONSIDERED NORMAL FOR A PREMATURE BABY AT THE AGE OF 1 WEEK?

- not less than 120–130 g/l
- + not less than 160–180 g/l

47. CLINICAL MANIFESTATIONS OF FETAL HEPATITIS ARE THE FOLLOWING SIGNS, EXCEPT:

- jaundice
- enlargement of the liver
- dark urine
- + coarse systolic murmur
- discolored stool

48. SIGNS OF HEMOLYTIC DISEASE OF THE NEWBORN DO NOT APPLY:

- jaundice
- anemia
- + hemorrhagic rash
- reticulocytosis
- increase in the level of indirect bilirubin

49. WHEN CARRYING OUT PHOTOTHERAPY THE SIMULTANEOUS PURPOSE IS PATHOGENETICALLY SHOWN:

- +additional fluid injection
- hydrocortisone
- cocarboxylases
- albumin
- saline solution

50. IN NEWBORN HYPERBILIRUBINEMIA, NUCLEAR JAUNDICE IS POSSIBLE TO DEVELOP, IF THE LEVEL OF INDIRECT BILIRUBIN IS INCREASED:

- up to 56 $\mu\text{mol/l}$
- up to 100 $\mu\text{mol/l}$
- up to 150 $\mu\text{mol/l}$
- up to 250 $\mu\text{mol/l}$
- + more than 340 $\mu\text{mol/l}$

SITUATIONAL TASKS FOR SELF-CONTROL

TASK#1

A Rh-positive mother with blood type A (II) was born to a Rh-positive mother with blood group O (I) from the first pregnancy, which proceeded without any features. Delivery on time, duration 15 hours. Departure of amniotic fluid 2 hours before delivery. The child was born with an Apgar score of 7/8 points, weighing 3000 g, 50 cm long. In the middle of the second day of life, a mild yellow skin staining appeared. On the 4th day, jaundice intensified, the child became lethargic, the sucking reflex, muscle tone, and tendon reflexes noticeably decreased. The level of bilirubin is 300 $\mu\text{mol/l}$, the reaction is indirect. Erythrocytes – $4.3 \times 10^{12}/\text{l}$, hemoglobin – 130 g/l, color. pok. – 0.9, Reticulocytes – 10 %, leukocytes – $18 \times 10^9/\text{l}$, e – 2 %, u – 1 %, p – 4 %, s – 43 %, l – 40 %, m – 10 %, ESR – 12 mm/h.

EXERCISE:

1. Your diagnosis.
2. What additional studies should be carried out to clarify the diagnosis?
3. List the diseases with which it is necessary to make a differential diagnosis.
4. Write out a prescription for a drug that has a cytoprotective effect.

TASK #2

The boy was born from IV pregnancy, which proceeded with gestosis of the first half, 2 births, on time, with an Apgar score of 7/8 points, weighing 3000 g, 50 cm long, the mother has Rh-negative blood of the A (II) group. From the first birth, the child is healthy, the second and third pregnancies ended in medical abortion. After 12 hours, the child's condition is severe: icteric staining of the skin, sclera, lethargy, regurgitation, decreased physiological reflexes and muscle tone, muffled heart sounds. The liver protrudes from under the edge of the costal arch by 4 cm, the spleen by 2 cm, the urine is dark in color. The child's blood is Rh-positive, group A (II). Blood test: erythrocytes – $4 \times 10^9/\text{l}$, Hb – 140 g/l, reticulocytes – 10 %, color. pok. – 1.0, leukocytes – $26 \times 10^9/\text{l}$, e – 0 %, m – 1 %, p – 14 %, s – 50 %, l – 25 %, m – 8 %, ESR – 12 mm/h. The level of indirect bilirubin is 310 $\mu\text{mol/l}$.

EXERCISE:

1. Your diagnosis.

2. What additional studies should be carried out to clarify the diagnosis?

3. List the diseases with which it is necessary to make a differential diagnosis?

4. What specialists should carry out dispensary observation of this child after discharge from the maternity hospital?

TASK#3

Child K., 5 days old, was transferred to the neonatal pathology department from the maternity hospital with the mother's complaints of jaundice of the skin, decreased appetite, and lack of weight gain. From the anamnesis it is known that on the 3rd day of life the child developed jaundice of the skin, which was regarded as physiological jaundice. In the following days, he began to suck sluggishly, did not add weight, the yellowness of the skin increased. Born from the first pregnancy. At the 3rd month of pregnancy, the mother suffered from acute bronchitis. Birth weight 3200 g, body length 52 cm. Cried immediately after birth. Apgar score – 7/8 points. Attached to the breast after 2 hours. Cord residue in bracket, physiological weight loss was 10 %. Upon admission, the patient is in a serious condition, sluggish, sucks out 30–40 ml of breast milk. Correct physique. Weight 2900 g. Cord residue in bracket. Above the lungs percussion pulmonary sound, auscultatory-puerile breathing. The boundaries of the heart correspond to the age, the heart sounds are muffled, rhythmic. The liver is dense, palpated 4 cm below the costal arch, the spleen – 2 cm, the stool is discolored, the urine is dark in color. Reflexes of the neonatal period are preserved. No focal neurological symptoms were identified. Additional examination data: erythrocytes – $5.4 \times 10^{12}/l$, Hb – 161 g/l, ESR – 4 mm/h. Total bilirubin – 171.04 $\mu\text{mol}/l$, direct – 121.02 $\mu\text{mol}/l$, indirect – 50.02 $\mu\text{mol}/l$, ASAT – 2.0 mmol/l, ALaT – 3.5 mmol/l, reaction to bile pigments positive in urine. Stercobilin was not found in the feces.

EXERCISE:

1. Formulate a clinical diagnosis.
2. List the main clinical symptoms that confirm your diagnosis.
3. List the main laboratory parameters confirming the specified diagnosis.

TASK #4

Girl O., 4 days old, is in the maternity hospital. From the anamnesis it is known that the child is from the first pregnancy, which proceeded with

preeclampsia in the first half. Delivery is urgent. Birth weight 3100 g, body length 51 cm, Apgar score 8/9 points. She screamed right away, she was attached to the chest in the delivery room, she sucked well. On the 3rd day icterus of the skin appeared. On examination on the 4th day of life, the condition is satisfactory, sucks well, the cry is loud. The skin is clean, moderately icteric, the umbilical wound is clean. In the lungs, breathing is puerile, heart sounds are sonorous, the abdomen is soft, the liver is +1 cm, the spleen is not enlarged. Yellow feces. Physiological reflexes are evoked, muscle tone is satisfactory. Mother's blood group A (I) Rh-positive. The child's blood group is O (I) Rh-positive. Complete blood count: erythrocytes – $5.9 \times 10^{12}/l$, Hb – 196 g/l, color. p. – 0.94, reticulocytes – 1.5 %, leukocytes – $9.0 \times 10^9/l$, e – 1 %, p/i – 5 %, s – 42 %, l – 47 %, m – 5 %, ESR – 2 mm/hour. General urine analysis: color – straw yellow, reaction – acidic, relative density – 1004, no protein, squamous epithelium – a little, leukocytes – 2–3 in p/sp, erythrocytes – no, cylinders – no. Biochemical blood test on the 4th day of life: total protein – 52.4 g/l, indirect bilirubin – 140 $\mu\text{mol}/l$, direct – no, ALaT – 0.25 mmol/l, ASAT – 0.18 mmol/l.

EXERCISE:

1. Make a diagnosis.
2. Evaluate the results of the complete blood count.
3. Evaluate the results of a general urine test.
4. Evaluate the results of a biochemical blood test. With what are the identified changes related?
5. Does this child require treatment for jaundice?
6. How to feed this baby?
7. What is the prognosis for this child?

TASK #5

Boy A., 4 days old, was admitted to the neonatal pathology department from the maternity hospital because of severe jaundice. From the anamnesis it is known that the child is from a 23-year-old woman with Rh-negative blood type O (I). The father of the child has a Rh-negative blood type A (II). The first pregnancy ended in a medical abortion at 10 weeks, the real pregnancy – the second, proceeded with preeclampsia in the second half. Delivery is urgent. Birth weight 3200 g, length 52 cm. He screamed immediately, a loud cry. By the end of the first day, icterus of the skin and sclera was noted. On the second day, the jaundice worsened. Upon admission to the hospital, the patient's condition was severe, severe icterus

of the skin and sclera, the child was lethargic, muscle hypotonia and hyporeflexia were noted. The liver protrudes from under the edge of the costal arch by 2.5 cm, the spleen at the costal edge. Transitional chair. Complete blood count: erythrocytes – $3.9 \times 10^{12}/l$, Hb – 141 g/l, color. p. – 0.99, leukocytes – $9.4 \times 10^9/l$, e – 1 %, p/i – 7 %, s – 53 %, l – 32 %, m – 7 %, ESR – 2 mm/hour. Biochemical analysis of blood on the 2nd day of life: total protein – 54.4 g/l, indirect bilirubin – 180 μmol , direct – no.

EXERCISE:

1. Make and justify the diagnosis.
2. What examinations should be carried out additionally to clarify the diagnosis?
3. What are the possible results of an additional examination?
4. What results can be obtained from abdominal ultrasound?
5. With what diseases should a differential diagnosis be made in this case?
6. Give treatment.
7. What health group should this child be assigned to after recovery?

TASK #6

Girl V., 3 days old, is in the maternity hospital. From the anamnesis it is known that the mother is 21 years old, she has a Rh-negative blood type A (II). The first pregnancy ended in childbirth 2 years ago, the child is healthy, has a Rh-negative blood type O (I). This pregnancy is the second, proceeded with swelling on the legs in the third trimester. Delivery is urgent. The first period is 6 hours 30 minutes, the second – 20 minutes, the anhydrous period is 4 hours 10 minutes. Birth weight 3400 g, body length 53 cm, Apgar score 7/8 points. She screamed at once, a loud cry. At the age of 12 hours, icteric coloration of the skin appeared. Conducted infusion and phototherapy. On examination on the 3rd day of life: the skin is intensely yellow with a greenish tint, the sclera are icteric, the umbilical wound is dry, puerile breathing in the lungs, no wheezing, heart sounds are clear, the abdomen is soft, the liver protrudes from under the costal arch by 3.5 cm, the spleen by 1 cm, the urine has an intense color, the physiological reflexes of the newborn are reduced. Complete blood count: erythrocytes – $4.2 \times 10^{12}/l$, Hb – 152 g/l, reticulocytes – 6 %, color. p. – 0.99, leukocytes – $12.0 \times 10^9/l$, e – 1 %, p/i – 6 %, s – 49 %, l – 36 %, m – 8 %, ESR – 2 mm/hour. The child's blood group is A (II) Rh-positive. Biochemical blood test on the 4th day of life: total protein – 54.8 g/l, indirect bilirubin – 328 $\mu\text{mol}/l$, direct bilirubin – 34 $\mu\text{mol}/l$, urea – 4.2 mmol/l, cholesterol – 7.0 mmol/l, potassium –

4.6 mmol/l, sodium – 138 mmol/l, calcium – 1.2 mmol/l, ASAT – 65 units, ALAT – 71 units, alkaline phosphatase – 350 units.

EXERCISE:

1. What disease can be thought of in this case?
2. Evaluate the results of the complete blood count.
3. Evaluate the results of a biochemical blood test.
4. What additional examination should the child undergo to confirm the diagnosis?
5. What results can be expected from abdominal ultrasound?
6. Give treatment.
7. How should the child be observed by the district pediatrician after discharge?

TASK #7

Child M., a full-term girl, born to young parents. Mother, 28 years old, nurse, considers herself healthy. Blood group B (III), Rf (+) floor. Father, 30 years old, a builder, considers himself healthy. The mother's pregnancy is the second, in the anamnesis – a medical abortion. The course of this pregnancy is complicated by repeated episodes of the threat of miscarriage, hyperandrogenism, and edematous form of preeclampsia. Childbirth independent in the period of 40–41 weeks, fast. Apgar score 7/8 points. After birth, a cephalohematoma was found in the right parietal region. 2 hours after birth, the baby was transferred to the "mother and child" ward for breastfeeding. At the age of 2 days. 7 hours of life was admitted to the neonatal pathology department due to the progression of jaundice. When transferred to the department, the level of bilirubin in the blood serum was 233.50 $\mu\text{mol/l}$ (direct – 5.10 $\mu\text{mol/l}$, indirect – 228.4 $\mu\text{mol/l}$). In the following days of life, further progression of jaundice was noted against the background of infusion and phototherapy. There were elements of a petechial rash, a hematoma in the right elbow area. Increased symptoms of toxicosis: lethargy, inhibition of the sucking reflex, regurgitation. On examination, attention was drawn to the dryness of the skin, its earthy-gray tint against the background of jaundice, dullness of heart tones, an increase in the size of the liver up to 4–4.5 cm below the edge of the costal arch, a dense consistency of the liver, and bright yellow urine. The dynamics of the level of bilirubin was as follows: 5 days – 357.87 $\mu\text{mol/l}$ (direct – 7.60 $\mu\text{mol/l}$, indirect – 350.27 $\mu\text{mol/l}$); 7 days – 406.09 $\mu\text{mol/l}$ (direct – 10.15 $\mu\text{mol/l}$, indirect – 395.94 $\mu\text{mol/l}$); 8 days – 458.2 $\mu\text{mol/l}$ (direct – 78.3 $\mu\text{mol/l}$, indirect – 379.8 $\mu\text{mol/l}$); 9 days – 496.6 $\mu\text{mol/l}$ (direct – 113,

1 $\mu\text{mol/l}$, indirect – 383.5 $\mu\text{mol/l}$). Biochemical blood test: total protein – 55 g/l; sugar – 3.0 mmol/g; ACT – 112.4 U/l (norm – up to 80 U/l); ALT – 82.8 U/l (norm – 47 U/l); γ – glutamyl transferase – 105.9 U/l (normal). Ultrasound examination of the abdominal organs: hepatomegaly, increased ECHO density of the liver. On the 12th day of life, information was received from the medical genetic center about the positive results of screening for galactosemia in the observed child. The child was transferred to artificial feeding with mixtures based on ionic protein hydrolysis. Continued infusion and phototherapy. On the 24th day of life, the level of bilirubin was 48 $\mu\text{mol/l}$ (direct – 10.65 $\mu\text{mol/l}$, indirect – 37.6 $\mu\text{mol/l}$). The child was discharged home.

EXERCISE:

1. What clinical variant of hyperbilirubinemia did this patient have?
2. What clinical data confirm the genesis of jaundice?
3. What laboratory parameters confirm the diagnosis?
4. Give advice on feeding your baby.

Go to problem 1

1. Diagnosis: hemolytic disease of the newborn according to the ABO system, moderate severity, icteric-anemic form.
2. Biochemical analysis: bilirubin with fractions, sugar, AST, ALT. Complete blood count: monitoring the level of hemoglobin, erythrocytes, hematocrit, hourly increase in bilirubin. Determine the immunoglobulins in the blood serum of the newborn (JgM, JgG, JgA). Coombs test. Analysis of urine.
3. Differential diagnosis: hyperbilirubinemia caused by a primary violation of the excretion of conjugated bilirubin (obstructive jaundice). Hyperbilirubinemia due to a combined dysfunction of hepatocytes (hepatic jaundice). Hyperbilirubinemia against the background of hemolytic anemia. Bilirubin encephalopathy and kernicterus.

Go to problem 2

1. Diagnosis: hemolytic disease of the newborn according to the Rh-factor system, moderate severity, icteric form.
2. Biochemical analysis: bilirubin with fractions, sugar, AST, ALT. Urinalysis: monitoring the level of hemoglobin, erythrocytes, hematocrit. Hourly increase in bilirubin. Determine the immunoglobulins in the blood serum of the newborn (JgM, JgG, JgA). Coombs test. Analysis of urine.

3. Differential diagnosis: hyperbilirubinemia caused by a primary violation of the excretion of conjugated bilirubin (mechanical jaundice); hyperbilirubinemia due to a combined dysfunction of hepatocytes (hepatic jaundice): congenital infectious hepatitis, sepsis; hereditary hepatitis: cystic fibrosis, galactosemia; hyperbilirubinemia against the background of other hemolytic jaundices (congenital microspherocytic anemia of Minkowski-Choffard, insufficiency of the enzyme glucose-6-phosphate dehydrogenase, polycythemic, etc.); bilirubin encephalopathy and kernicterus.

4. Dispensary observation of children who have had hemolytic disease of the newborn is carried out by a pediatrician together with a neurologist, ophthalmologist, otolaryngologist. The frequency of preventive examinations by a pediatrician in the first year of life is 2 times a month, in the second – 1 time per month and in the third – 1 time in 3 months. Within 3 months after birth, a monthly blood test (hemoglobin, erythrocytes, reticulocytes) is required. Prevention of anemia. Preventive vaccinations according to indications and after consultation with an immunologist.

Go to problem 3

1. Diagnosis: neonatal jaundice, viral hepatitis, cytotoxic syndrome, cholestasis syndrome.

2. Symptoms: intoxication, hepatosplenomegaly, acholic stool, dark urine, icterus of the skin.

3. Laboratory data:

- hyperbilirubinemia (total bilirubin – 171 mmol/l, predominantly direct bilirubin – 121.02 μ mol/l, increased liver enzymes – AST and ALT, a decrease in the de Rittis coefficient);
- the reaction to bile pigments in the urine is positive;
- absence of stercobilin in feces.

Go to problem 4

1. Transient hyperbilirubinemia. The diagnosis was made on the basis of anamnesis data (favorable course of pregnancy and childbirth, the appearance of icterus of the skin on the 3rd day of life, the absence of data for a possible Rh-conflict or conflict according to the ABO system); objective status: on the 4th day of life, the condition is satisfactory, there is no hepatosplenomegaly, as well as other indicators are normal; laboratory data – complete blood count and urinalysis within the age norm, in the biochemical blood test the level of indirect bilirubin is 140 μ mol/l, which is acceptable on the 4th day of life in full-term newborns, direct bilirubin is absent.

2. Indicators of the general blood test – within the age norm.
3. Indicators of the general analysis of urine – within the age norm.
4. Indicators of a biochemical blood test: the level of indirect bilirubin is 140 $\mu\text{mol/l}$ and the absence of a direct fraction is acceptable for the 4th day of life, normally up to 171 $\mu\text{mol/l}$. The rest of the parameters are normal. Such an increase in the level of indirect bilirubin is due to a number of factors: a shortened lifespan of erythrocytes due to the predominance of erythrocytes with fetal hemoglobin, pronounced ineffective erythropoiesis. Increased production of bilirubin in the catabolic phase of metabolism from non-erythrocyte sources of heme (myoglobin, hepatic cytochrome, etc.). Decreased uptake of indirect bilirubin by hepatocytes. The low ability to glucuronate bilirubin due to the low activity of glucuronyl transferase and uridine diphosphoglucose dehydrogenase, mainly due to their suppression by the mother's hormones. Reduced ability to excrete bilirubin from the hepatocyte. Increased intake of indirect bilirubin from the intestine.
5. Jaundice in this child is physiological and does not require treatment.
6. If the mother has sufficient lactation (not indicated in the condition of the problem), breastfeeding is indicated for this child.
7. The prognosis is favorable, physiological jaundice disappears by the end of the first week of life and does not harm the health of the child.

Go to problem 5

1. Hemolytic disease of the newborn (conflict according to the ABO system), anemic form, course of moderate severity. The diagnosis was made on the basis of anamnesis data: mother's blood group O (I), Rh-negative, father's blood group – A (II), Rh-negative. HDN according to the ABO system occurs in newborns born to mothers with the first blood group, icterus of the skin and sclera on the first day of a child's life, increased jaundice on the second day (appearance on the first day of life is a sign of pathological hyperbilirubinemia). Objective examination data – a serious condition, severe icterus, lethargy, hypotension, hyporeflexia, hepatosplenomegaly. Laboratory data – signs of hemolytic anemia in the general blood test (decrease in the level of hemoglobin, erythrocytes).
2. In addition, it is necessary to determine the child's blood group, a peripheral blood test with counting the number of reticulocytes, a dynamic determination of the concentration of bilirubin in the child's blood serum. It is also possible to conduct immunological studies: determination of the titer of allohemagglutinins in the blood and mother's milk; indirect Coombs test.

3. Most likely, the child will have A (II), Rh-negative blood type, an increased number of reticulocytes, the Coombs test will be weakly positive (with a Rh-conflict, it is pronounced, positive).

4. Ultrasound of the abdominal organs can reveal hepatosplenomegaly, possibly the presence of free fluid in the abdominal cavity (in the case of edematous form of HDN).

5. This disease should be differentiated from physiological jaundice, HDN with Rh-incompatibility, hemolytic anemia.

6. Treatment: taking into account the level of indirect bilirubin ($180 \mu\text{mol/l}$), the level of hemoglobin (141 g/l), this child is shown: feeding with an adapted milk formula, maintaining an optimal temperature regime, constant phototherapy, monitoring the level of hemoglobin, bilirubin and its hourly increase, as well as preparation for a replacement blood transfusion in the event of a further hourly increase in bilirubin over $6.8 \mu\text{mol/l}$ per hour.

7. Health group – 3.

Go to problem 6

1. In this case, we can think of hemolytic disease of the newborn (conflict on the Rh-factor), P55.0, icteric form, severe course, given the mother's blood group O (II) (Rh-negative), the child's blood group O (I) (Rh-positive), the dynamics of the development of jaundice and laboratory examination data. However, the greenish tint of the skin, the presence of direct bilirubin also allows us to think about obstructive jaundice, a syndrome of thickening of bile.

2. In the general blood test – signs of hemolysis: a decrease in the level of hemoglobin, the number of erythrocytes, an increase in the number of reticulocytes.

3. In a biochemical blood test – a sharp increase in the level of indirect bilirubin (close to the level of bilirubin at the risk of bilirubin encephalopathy), the presence of direct bilirubin, an increase in cholesterol, liver enzymes, which indicates involvement in the pathological process of the liver.

4. A Coombs test should be performed (should be sharply positive), as well as a general urinalysis, check the level of GGT, cholesterol, beta – lipoproteins, bile acids, albumin, fibrinogen, PTI – in order to exclude hyperbilirubinemia associated with infectious, toxic or metabolic damage to the liver; as well as ultrasound of the abdominal organs in order to visualize the structure of the liver, gallbladder – exclusion of obstructive jaundice.

5. Ultrasound of the abdominal organs can reveal an increase in the size of the liver, various malformations of the biliary tract, an increase in the gallbladder if there is an obstruction to the outflow of bile.

6. If the diagnosis of HDN (Rhesus factor conflict) is confirmed, it is possible to breastfeed, maintain an optimal temperature regime, phototherapy and exchange transfusion (2 BCC replacement). If jaundice is of a different nature, in addition to the above measures, the cause of cholestasis should be eliminated and resolved breast-feeding.

7. Plan:

- Transfer of the child to a specialized department for additional examination. After discharge: OAC after dynamics in 7–10 days, blood bilirubin concentration in dynamics 1 time per week, OAM with a study of bile pigments.

- Consultations of a neuropathologist, ENT, ophthalmologist, speech therapist.

Go to problem 7

1. The clinical variant of hyperbilirubinemia is associated with classical galactosemia, the most severe form of galactose metabolism disorder caused by a deficiency in the activity of the GALT enzyme (galactose 1-phosphate uridylyltransferase). The disease usually manifests itself in the first days, weeks of life, progresses rapidly against the background of breastfeeding.

2. The diagnosis is confirmed by the following clinical data: an increase in symptoms of toxicosis with signs of lethargy, inhibition of the sucking reflex, regurgitation, muscle hypotension, progression of jaundice, hepatomegaly, elements of a petechial rash, hematoma in the right elbow region. Improvement in the child's condition and the disappearance of the clinical symptoms of the disease when transferred to artificial feeding with special mixtures also confirms the clinical diagnosis and makes the prognosis more positive. It is necessary to consult an ophthalmologist in order to exclude cataracts.

3. The following laboratory parameters confirm the diagnosis: positive results of screening for galactosemia (determination of the level of total galactose in dried blood spots: borderline values of 7.2–10 mg/dl and more than 10 mg/dl – a positive result and a decrease in the activity of the GALT enzyme in dried spots blood <2.5 U/gHb). An increase in the activity of transaminases in the blood serum and an increase in the concentration of bilirubin (unconjugated hyperbilirubinemia, characteristic of the early stage of the disease, then turns into conjugated); ultrasound examination of the abdominal organs: hepatomegaly, increased ECHO density of the liver. The presence of inflammatory changes in peripheral blood tests, in combination

with an increase in the level of C-reactive protein and a positive procalcitonin test, is a criterion for the addition of sepsis.

4. The main method of treatment for galactosemia is diet therapy, which provides for a life-long exclusion from the diet of products containing galactose and lactose. It is necessary to completely exclude from the patient's diet any kind of milk (including women's, cow's, goat's, baby milk formulas, etc.) and all dairy products, and also in the future to strictly avoid the use of those products where they can be added (bread, pastries, sausages, caramel, sweets, margarines, etc.). It is also forbidden to use low-lactose milk and mixtures. Mixtures based on soy protein isolate are used, in which vegetable galactosides are completely absent: Nutrilak Soy, Nutrilon Soy, Enfamil Soy. It is possible that allergic reactions to soy protein may occur, and in such cases it is advisable to prescribe mixtures based on casein hydrolysates: Pregestimil, Nutramigen. Lactose-free milk formulas containing 50–60 % whey proteins in the protein component should not be used for dietary therapy in infants with galactosemia in infancy, as they may contain trace amounts of galactose. It is possible to use only casein-predominant lactose-free milk mixtures: Enfamil, Laktofri.

CLINICAL CASE NO.1

Girl A. from 1 urgent delivery in cephalic presentation, at 40.5 weeks (if the mother had primary weakness of labor, anemia of the 1st degree, VSD of the hypotonic type, chronic cystitis in remission; the anhydrous period was 6 hours 15 minutes, water front-light, rear-green; duration of the 1st period – 5 h 15 min, 2nd period – 15 min), with a weight of 3200 g, height 50 cm, head circumference 34 cm, chest circumference 33 cm, was born in a satisfactory condition. She screamed after sanitation of the upper respiratory tract. The scream is loud. The skin is pink, clean, in a plentiful green lubrication. Visible mucous membranes are pink, clean. Cord remnant under the bracket. The head is rounded, the size of the large fontanelle is 1.5×1.5 cm, it is not tense. The shape of the chest is cylindrical. Breathing in the lungs is puerile, respiratory rate 40 per minute. Rhythmic heart sounds clear, heart rate 148 per minute. The abdomen is soft, palpable, the liver is +1.5 cm from under the costal arch, the spleen is not palpable. Muscle tone is sufficient. The physiological reflexes of the newborn are evoked. The external genital organs are formed according to the female type. Anus formed. Stool – meconium plentiful, urination was not. Breeding the legs in the hip joints in full. Apgar score: 7/8 b. Resuscitation assistance was not carried out.

Mother's age is 30 years. 1 pregnancy – real, proceeded against the background ureaplasmosis in the period of 17–18 weeks of pregnancy (treated – polygynax, vilprafen); ARVI in the 2nd half of pregnancy, which proceeded with an increase in temperature up to 37.3 degrees (treated with symptomatic drugs). The mother has past and chronic diseases: chronic cystitis (in remission), VVD of a mixed type from the age of 15, acute respiratory infections, rubella, tonsillitis. Bad habits denies during pregnancy. Heredity is not burdened. There were no operations or blood transfusions. The allergic anamnesis is aggravated by reactions to the administration of antispasmodic drugs (spazgan, spazmolgon) in the form of a sharp decrease in blood pressure and rash. Husband's health: 28 years old, healthy (from the words), civil marriage, smokes. Does not abuse alcohol. Epidemiological history without features.

Mother's blood group and Rh-factor O (I) Rh + (positive). Gr. Child's blood: B (III) Rh(+)pol. Through 1 hour 30 minutes after birth. In the biochemical analysis of umbilical cord blood, indirect bilirubin was found - $63.84 \mu\text{mol/l}$, with total bilirubin – $69.13 \mu\text{mol/l}$, and the child from the delivery room is in a state of moderate severity due to the early

implementation of hemolytic disease of the newborn (HDN) according to the ABO factor to the department of pathology of newborns (stage 2 of nursing) with a diagnosis of ABO-isoimmunization of the fetus and newborn (P55.1), icteric form, moderate course.

On admission general condition of moderate severity. There are no signs of respiratory failure (RD). There are no signs of bilirubin intoxication. The scream is loud. Actively shows hunger anxiety. The skin is pink with a subicteric tinge. There are no edema. Visible mucous membranes are clean. Correct physique. The subcutaneous fat layer is evenly developed. The clavicles are intact. In the pharynx calmly. Nasal breathing is free. The umbilical cord remains under the bracket, is held. Peri-umbilical area without signs of inflammation. The head is rounded. Breathing is independent, puerile, carried out in all fields, no wheezing. BH – 54 per minute. Pulse on *a. radialis* and femoral arteries rhythmic. Heart sounds are rhythmic, muffled. Heart rate – 132 per minute. The abdomen is soft, palpation is available. Peristalsis is heard. Liver on the edge of the costal arch. The spleen is not palpable. There was no chair. Didn't urinate. The genital organs are formed according to the female type, correctly. Status of the hip joints: full dilution.

Neurological status: Large fontanel 1.0 cm × 1.0 cm is not tense. Opens eyes. Motor activity is moderately reduced. Muscle tone corresponds to gestational age. Physiological reflexes are evoked. Pathological foot signs are negative. FMN – palpebral fissures, pupils D = S. The photoreaction of pupils is saved. Swallowing, phonation are not disturbed. Tongue in the midline. Nasolabial folds are symmetrical. Tendon reflexes are alive. There are no meningeal symptoms. The Fenton TR score corresponds to the gestational age.

A complete clinical and laboratory examination was carried out. During 4 days of life, the general condition of the child remained moderate due to the course of hemolytic disease of the newborn and the implementation of hyperbilirubinemia in the form of icteric syndrome: yellowness of the skin and visible mucous membranes; positive Coombs test; there was an increase in the level of total bilirubin up to 323.89 $\mu\text{mol/l}$ due to the indirect fraction (317.38 $\mu\text{mol/l}$). The hemoglobin level remained within the physiological norm.

For medicinal purpose phototherapy was carried out with a constant course for 10 days. As a result of treatment the child's well-being improved, became more active, sociable. Sucks actively breast, feeding mode is free. Restored his birth weight. The skin is pink with a slight subicteric tinge.

Visible mucous membranes are clean. Nasal breathing is free. Umbilical wound in the stage of epithelialization. Peri-umbilical area without signs of inflammation. Neurological status: large fontanel 1.0 cm × 1.0 cm is not tense. Open eyes. Motor activity is preserved in full. Muscle tone corresponds to gestational age. Physiological reflexes are alive. Breathing is independent, puerile, carried out in all fields, no wheezing. Heart tones are rhythmic, clear. The abdomen is soft, palpation is available. Peristalsis is heard. Liver is on the edge of the costal arch. The spleen is not palpable. Stool on examination, yellow-green, granular. Urine is light. On day 11, total bilirubin reached 180.19 $\mu\text{mol/l}$.

A day later, without phototherapy, jaundice was visually minimal, with a transcutaneous examination of total bilirubin 103/104 $\mu\text{mol/l}$. Satisfactory the child was discharged home.

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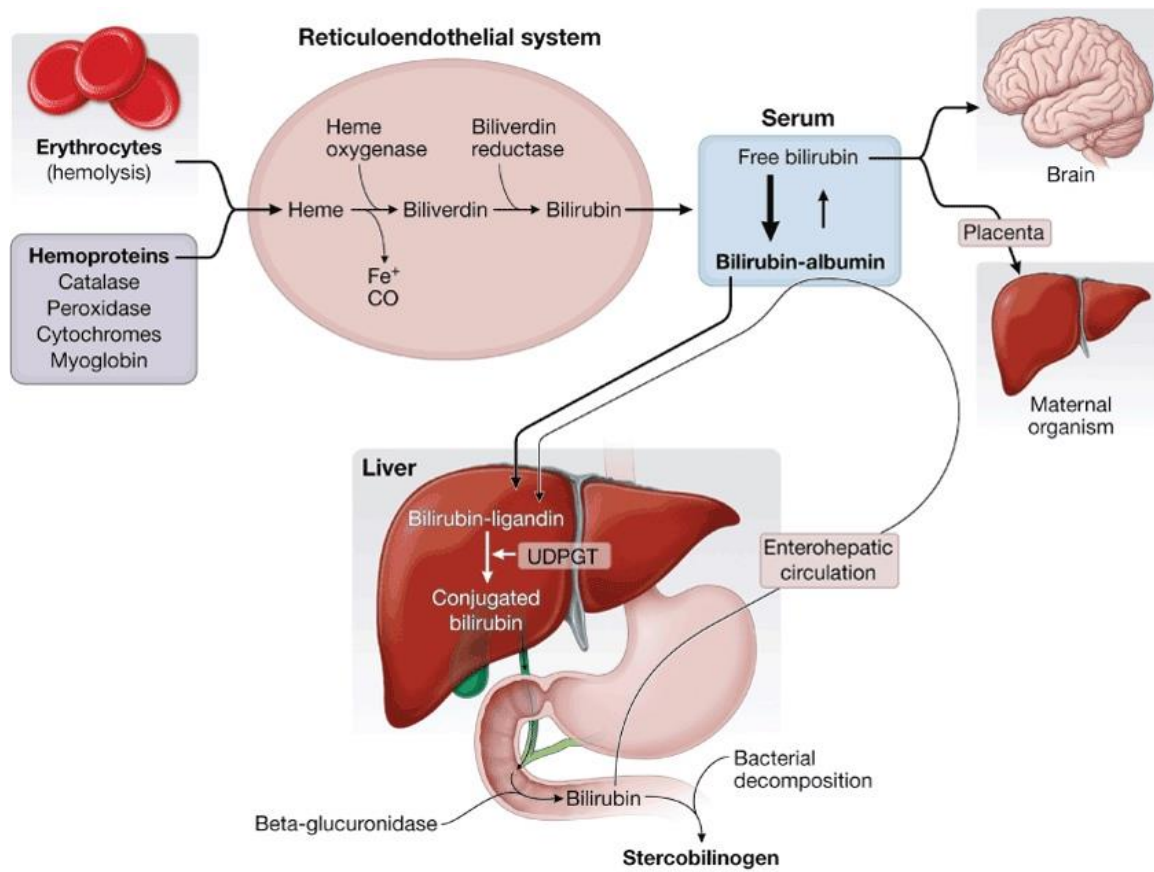
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APPLICATIONS

Application No. 1

Stages of bilirubin metabolism



Application No. 2

Characteristics of hemolytic disease due to ABO and Ph-incompatibility

Clinical symptoms	ABO-incompatibility	Ph-incompatibility
Possibility of antenatal screening	no	very important
Develops during the first pregnancy	often	rarely
Impact on subsequent pregnancies	various	negative
Direct Coombs reaction in cord blood	from – to ±	+++
Indirect Coombs reaction in cord blood	+	not necessary
Erythroblasts in the blood	+	+++
Reticulocytes in the blood	from + to ++	++
Spherocytes in the blood	++	±
Hepatosplenomegaly	+/-	++
Jaundice	varying degrees	Severity is directly related to the early rise in bilirubin and its hourly increase
Prevention	impossible	The introduction of anti-Ph-immunoglobulin Ph (-) mother after the birth of Ph (+) child
Early anemia	+/-	++
Late anemia	rarely	often

Application No. 3

CNS damage (bilirubin encephalopathy)

Light degree	Medium	Severe degree
Damage to the auditory or facial oculomotor nerve	The defeat of the subcortical regions with severe hyperkinesis	Spastic paresis, paralysis, hearing and speech violations
Satisfactory development of intelligence	Extrapyramidal muscle rigidity bilateral athetosis, psychomotor retardation	Bilateral athetosis with symptoms of torsion spasm Choreoathetosis – profound mental retardation
Delayed motor development		
Dispensary observation pediatrician, otolaryngologist, neuropathologist, speech therapist. Examination: Ultrasound of the brain. Treatment: exercise therapy, physiotherapy, vitamin B complex	Treatment and examination in specialized neuropsychiatric departments	Disabled from birth. Need social security
Vaccinations are contraindicated up to 1 year	Vaccinations are contraindicated up to 2–3 years. In the future, the issue of vaccinations is decided by the medical advisory commission	

Application No. 4

Anemia

At birth			Early			Late
Light (Ist) Hb 160–140 g/l	Moderate severity (IIst) Hb 140–120 g/l	Severe (III st) Hb 120–100 g/l	2–3 weeks I or II st	2–8 weeks I, II or III st	3–7 weeks after exchange transfusion II or III st	After 3 months of mixed anemia
Hyperregenerative, hemolysis exceeds hematopoiesis			Ist Hb120– 100 g\l	IIst Hb 100–80 g/l	IIIst Hb 80 g/l	
Treatment in the maternity ward or neonatal pathology department			Continued hemolysis by antibodies remaining in the blood and tissues	Reduced bone marrow activity, hemolysis exceeds hematopoiesis	Increased destruction of donor erythrocytes	
Doctor tactics	Anemia Ist (blood test after 10–14 days)		Proper care, breastfeeding, maximum exposure to fresh air. Complex of vitamins C, B1, B2, B6			
	Anemia IIst (blood test after 7–10 days)		Vitamin B12 – 50 mg every other day 10 doses			
	Anemia III st		Treatment in a hospital. RBC transfusion is indicated			

Vaccinations are contraindicated in the 1st year of life.

Application No. 5

Differential diagnosis of direct and indirect hyperbilirubinemia		
Clinical sign	Direct hyperbilirubinemia (cholestasis)	Indirect hyperbilirubinemia
Skin coloration	Icteric with a greenish or brown tinge	Icteric
Feces	Discolored (acholic), faintly colored or fragmented colored	Normal color
Urine	Dark ("beer color")	Normal color

Application No. 6

The main biochemical parameters necessary for the differential diagnosis of jaundice (according to S. Sherlock, J. Dooley, 1999)

Index	Normal values
Bilirubin total knitted (straight)	5–17 $\mu\text{mol/l}$ (0.3–1.0 mg%) less than 15 % of total bilirubin
Alkaline phosphatase	35–130 IU/l
ASAT	5–40 IU/L
ALAT	5–35 IU/l
G-glutamyl transpeptidase (GGTP)	10–48 IU/l
Albumen	35–50 g/hl
Y globulin	5–15 g/l
Prothrombin time (after intramuscular administration of vitamin K)	12–16 s

Application No. 7

Use of various treatments for jaundice in preterm infants (gestational age <37 weeks)

Body weight, g	The content of total bilirubin in blood serum, $\mu\text{mol/l}$ (and mg%)			
	No risk factor		Presence of a risk factor	
	Phytotherapy	Exchange transfusion	Phytotherapy	Exchange transfusion
<1000	85–119 (5–7)	170 (10)	68–102 (4–6)	
1001–1500	119–170 (7–10)	170–255 (10–15)	102–136 (6–8)	170–204 (10–12)
1501–2000	170 (10)	289 (17)	136–170 (8–10)	255 (15)
>2000	170–204 (10–12)	306 (18)	170 (10)	289 (17)

Application No. 8



Carrying out phototherapy for a premature baby with a photo-lamp + Bilisoft system



Carrying out phototherapy for a premature baby with the Bilisoft system. The level of total bilirubin is 220 mmol/l.



Carrying out phototherapy in a photo barrel for a child aged 4 days. The level of total bilirubin is 280 mmol/l.

Учебное издание

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FOR POTENTIAL DANGER**

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