Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

JAUNDICES OF NEWBORNS. DIFFERENTIAL DIAGNOSIS OF JAUNDICES

Methodical recommendations
for student's 5th and 6th courses of medical faculty in discipline
«Pediatrics, children infectious diseases»

Kharkiv – 2023

УДК 616.36-008.5-053.31-079/4(072)
J 28

Reviewers:

V. G. Chernusky – Doctor of Medicine, Full professor, Head of the Department of Pediatrics of the V. N. Karazin Kharkiv National University;

O. Yu. Belousova – Doctor of Medical Science, Full Professor, Head of Pediatric Gastroenterology and Nutrition, Kharkiv Medical Academy of Postgraduate Education.

Approved for publication by the decision of the Scientific and Methodical Council of V. N. Karazin Kharkiv National University (Protocol № 2 of November 15, 2023)

Jaundices of newborns. Differential diagnosis of jaundices : methodical recommendations
J 28 for student's 5th and 6th courses of medical faculty in discipline «Pediatrics, children infectious diseases» / compil. N. I. Rybak, K. V. Shtrakh. – Kharkiv : V. N. Karazin Kharkiv National University, 2023. – 24 p.

Methodical recommendations are worked out on the basis of the Program of discipline of «Pediatrics with children's infectious diseases» and «Pediatrics, children infectious diseases» for students of higher medical educational institutions of III–IV levels of accreditation, authorized by Ministry of Health of Ukraine. This recommendation is intended for the 5th and 6th years English-speaking medical students.

УДК 616.36-008.5-053.31-079/4(072)

Навчальне видання

Рибак Наталія Ігорівна
Штрах Катерина Василівна

**ЖОВТЯНИЦІ НОВОНАРОДЖЕНИХ.
ДИФЕРЕНЦІЙНИЙ ДІАГНОЗ ЖОВТЯНИЦЬ**

Методичні рекомендації
для здобувачів вищої освіти 5-го та 6-го років навчання з дисциплін
«Педіатрія, дитячі інфекційні хвороби», «Педіатрія з дитячими інфекційними хворобами»

(Англ. мовою)

Коректор *О. В. Анцибора*
Комп'ютерне верстання *В. В. Савінкова*
Макет обкладинки *І. М. Дончик*

Формат 60*84/16.Ум. друк. арк. 1,57. Наклад 50 пр. Зам. № 186/23.

Видавець і виготовлювач
Харківський національний університет імені В. Н. Каразіна,
61022, м. Харків, майдан Свободи, 4.
Свідоцтво суб'єкта видавничої справи ДК № 3367 від 13.01.2009
Видавництво ХНУ імені В. Н. Каразіна

CONTENTS

LIST OF ABREVIATIONS

RES – reticulo endothelial system
UDPG – uridine phosphoglucuranic acid
BDG – bilirubin dehydrogenase
IB – indirect bilirubin
TCB –transcutaneous bilirubinometry
TSB – total serum bilirubin
PCR – polymerase chain reaction
ALT – alanine aminotransferase
AST – aspartate aminotransferase
Hb – hemoglobin
Rh – rhesus factor
Er – erythrocytes

INTRODUCTION

Jaundice is one of the most common conditions that require medical attention in newborns. Neonatal jaundice is extremely common – almost every newborn has an increase in serum unconjugated bilirubin during the first week of life. Clinical manifestations of hyperbilirubinemia develop in approximately 60% of full-term and 80% of premature infants. The peculiarities of neonatal jaundice are that they can be physiological, occur in healthy children, but can be a manifestation of a number of diseases. Therefore, neonatal jaundice should always be considered a symptom of potential danger.

The urgency of jaundice in the neonatal period is due to the prevalence of jaundice among most newborns. It should be noted that jaundice accompanies many diseases, can be severe and fatal. In addition, early diagnosis and timely treatment of neonatal jaundice determine the prognosis of such diseases and prevent the development of complications. Based on the above, it is very important for medical students to be able to correctly and timely differentiate one type of jaundice from another.

DEFINITION AND PATHOGENESIS OF JAUNDICE

Neonatal jaundice it is the appearance of visible yellow color of the skin, sclera and / or mucous membranes of the child due to increased levels of bilirubin in the blood of the newborn.

It is clinically advisable to classify the jaundice of the newborn by the time of its appearance:

Early jaundice, which appears up to 36 hours of a child's life. Jaundice that appears in the first 24 hours is always a sign of pathology.

"Physiological" jaundice, which manifests itself after 36 hours of a child's life and is characterized by an increase in serum total bilirubin levels not higher than 205 μmol / l. Such jaundice is most often caused by the peculiarities of the development and metabolism of the newborn during this period of life. "Physiological" jaundice can have both uncomplicated and complicated course, so it requires careful monitoring of the child's condition. Complicated "physiological" jaundice is a physiological jaundice, the course of which may be accompanied by a change in the child's condition.

Prolonged jaundice, which is determined after 14 days of life in a full-term newborn and after 21 days of life in a premature baby.

Late jaundice, which appears after 7 days of life of the newborn. This jaundice always requires careful examination. In rare cases, the course of neonatal jaundice may be complicated by the development of bilirubin encephalopathy, which is manifested by acute lesions of the central nervous system. This can lead to irreversible chronic damage to the central nervous system called *nuclear jaundice.*

Considering that neonatal jaundice may be due not only to the physiological features of development and metabolism of the newborn, in some cases it is necessary to conduct a differential diagnosis to optimize the management of the child.

Pathogenesis. The pathogenesis of jaundice is based on the pathology of bilirubin metabolism. Newborn babies have a number of features of bilirubin metabolism, which cause a high frequency of this pathology. The source of bilirubin is hemoglobin of destroyed erythrocytes. In newborns, the lifespan of erythrocytes is shorter than in adults.

The formation of bilirubin occurs in the cells of the RES, from where it enters the bloodstream. This is indirect bilirubin, which is characterized by tropism to tissues rich in lipids, insolubility in water, toxic properties. In plasma, indirect bilirubin binds to albumin and is transported to liver cells.

Newborns have a lower level of blood protein, so part of the bilirubin remains in the free state and diffuses into the tissues, primarily into the subcutaneous tissue. The resulting jaundice is physiological.

The liver of newborns has a certain degree of immaturity, so the processes of conjugation of indirect bilirubin in the first days of life are slowed down. At 5-7 days of life, the enzymatic function of the liver becomes more active. Conversion of indirect bilirubin to direct occurs with the participation of glucuronic acid and enzymes UDPG-dehydrogenase, glucuronyltransferase, cytochrome P-450. The activity of enzymes is greatly influenced by drugs used during childbirth, as well as components of breast milk. Some unconjugated bilirubin enters the intestine, where it is actively absorbed into the bloodstream, maintaining hyperbilirubinemia. In addition, newborns have narrow bile ducts, low concentrations of bile acids. Delay in the elimination of meconium leads to the accumulation of bilirubin in the digestive tract, the transformation of direct bilirubin into indirect by intestinal beta-glucuronidase, increasing its toxic effects on the body. The concentration of indirect bilirubin in the blood above 340 μmol / l is dangerous for the life of the newborn, leads to the development of bilirubin encephalopathy.

CLINICAL AND LABORATORY CLASSIFICATION OF NEONATAL JAUNDICE (Oski F., 1991)

I. Jaundice with indirect hyperbilirubinemia

1. Hemolytic anemia:

a) hemolytic disease of newborns;

b) hereditary membranopathies, hemoglobinopathies and erythrocyte enzymopathy;

c) acquired (infectious, medicinal, microangiopathic).

2. Polycythemia.

3. Hematomas and clotted blood syndrome.

4. Children from mothers with diabetes.

5. Hereditary:

a) defects in bilirubin clearance;

b) symptomatic in hypothyroidism and other endocrinopathies, galactosemia, fructosemia and other metabolic abnormalities.

6. Decreased level of bilirubin excretion from the intestine and increased intestinal and hepatic bilirubin circulation:

a) jaundice of breastfeeding;

b) jaundice from breast milk;

c) jaundice with pylorostenosis;

d) jaundice with meconium Ileus;

e) jaundice with intestinal obstruction.

II. Jaundice with direct hyperbilirubinemia *(with a predominance in the serum of BDG****), but with a stool of normal color:***

1. Hepatitis (viral, bacterial, parasitic, fungal, toxic).

2. Hereditary metabolic abnormalities (galactosemia, fructosemia, tyrosinemia, Dubin-Jones syndrome, Rotor, Baylor, glycogen type IV disease, cystofibrosis, accumulation disease).

3. Complete atresia of the extrahepatic bile ducts:

a) the normal number of bile ducts;

b) reduced number of bile ducts.

4. Hypoplasia of the extrahepatic biliary tract:

a) the normal number of bile ducts;

b) reduced number of bile ducts.

5. Hepatitis without abnormalities of the biliary tract.

6. Bile thickening syndrome ("bile plug" syndrome), cholelithiasis.

7. Cyst of the bile duct or compression of the external biliary tract.

8. Cystic fibrosis and antitrypsin deficiency.

Information used for differential diagnosis of jaundice in newborns.

III. Jaundice with direct hyperbilirubinemia and discolored stools of varying severity (cholestatic jaundice)

1. Complete intrahepatic atresia of the biliary tract (without or with hepatitis):

a) normal extrahepatic bile ducts;

b) hypoplasia of the extrahepatic bile ducts;

Conjugative jaundice is a group of jaundices of various etiologies characterized by elevated levels of conjugated bilirubin in the blood.

Table 1

Pathogenetic classification

Pathogenetic mechanisms	Congenital	Acquired
Low uptake of bilirubin by hepatocytes	Gilbert's syndrome	
No or decreased bilirubin conjugation	Kriegler's-Nayara syndrome I, II type, Arias – Lucia-Driscola syndrome	Jaundice during breastfeeding ("jaundice from breast milk")
Disorders of bilirubin excretion from the hepatocyte	Dubin-Jones and Rotor syndromes	Hepatitis (infectious, toxic), hematological disorders, parenteral breastfeeding
Symptomatic	With hypothyroidism, galactosemia, tyrosinase	

Gilbert's syndrome

Etiology. The type of inheritance is autosomal dominant.

Pathogenesis. Violation of bilirubin uptake by hepatocytes or conjugation of indirect bilirubin with glucuronic acid is due to hereditary inferiority of the glucuronyltransferase system. The cause of hyperbilirubinemia is considered to

be a decrease in the penetration of IB into the hepatocyte (up to 30% of normal), although at the same time there is a slight decrease in the activity of hepatic glucuronyltransferase. That is why the positive effect of phenobarbital therapy is noted in Gilbert's disease - the intensity of jaundice decreases or it disappears. Usually, the diagnosis is made in school or even in adolescence. Analysis of the anamnesis in patients shows that about half of them had severe jaundice in the neonatal period.

The diagnosis can be suspected accidentally during a preventive examination - the detection of moderate jaundice with NB and the absence of enlargement of the liver, spleen, signs of increased hemolysis.

The prognosis is favorable.

Kriegler-Nayar syndrome (type I and II)

Etiology: type of inheritance autosomal recessive.

Pathogenesis: glucuronyltransferase enzyme deficiency.

Clinic: jaundice appears 1-3 days after birth. Bilirubin can rise to high numbers (600 - 765 mmol / l), which leads to the development of nuclear jaundice. There is no enhanced hemolysis of erythrocytes. Liver function tests are normal.

Prognosis: doubtful. Children often die in the first months and years of life. During survival, elevated bilirubin levels persist throughout life.

Dubin-Jones and Rotor syndrome

Etiology: type of inheritance autosomal recessive.

Pathogenesis: deficiency of bilirubin excretion through the hepatocyte wall.

Clinic: the disease is accompanied by a moderate increase in direct bilirubin, some increase in the liver, a marked increase in urinary excretion of coproporphyrins. At Dubin-Jones syndrome there is a deficiency of canalicular secretion of BDG.

Prognosis: with both syndromes – favorable.

Jaundice intermittent

Intermittent jaundice, exacerbated by intercurrent disease or after starvation, the appointment of paracetamol. The diagnosis is made on the basis of long-term indirect hyperbilirubinemia, pedigree analysis, exclusion of other causes of hyperbilirubinemia.

Clinic: similar to transient jaundice, but no signs of hemolysis. There are no pronounced changes on the part of the internal organs, the color of feces and urine is normal.

The prognosis is favorable.

Luce-Driscol syndrome

It is a deep, but transient, neonatal defect of glucuronyltransferase activity; inherited by autosomal recessive type. The serum of mothers of such children contains an inhibitor of glucuronyltransferase activity (4-10 times more active than in the serum of pregnant women). Hyperbilirubinemia (dominated by NB) develops in the first days of life, can be very pronounced and lead to nuclear jaundice. If artificial blood transfusion, phototherapy are carried out in time, the prognosis is favorable, and jaundice disappears without a trace at about the 2nd week of life, i.e. bilirubin conjugation inhibiting factor, most likely one of the hormones of pregnancy. **The diagnosis** is made on the basis of exclusion of other hyperbilirubinemias, the analysis of the family anamnesis.

Jaundice in hepatitis

Etiology: TORCH – infection, sepsis, toxic substances, viral hepatitis

Pathogenesis: impaired conjugation of indirectly affected hepatocytes.

Clinic: the duration of jaundice depends on the etiology of hepatitis. The general condition of the child is disturbed (poor appetite, vomiting, impaired sucking and swallowing, poor weight gain, bloating, lethargy). Hepatomegaly is palpated, the edge of the liver is dense. The color of the stool changes: urine becomes dark, feces - light. In some patients, the clinical picture may be dominated by signs of cholestasis, cytolysis of hepatocytes, in severe cases of liver failure. Liver function tests are impaired.

Jaundice during breastfeeding ("jaundice from breast milk")

Etiology: the presence of 3%-20% pregnandiol in breast milk, prescribing drugs to the mother (oxacillin, gentamicin, acetylsalicylic acid, sulfonamides, fatty acids, etc.).

Pathogenesis: in the first case, the metabolite inhibits the activity of glucuronyltransferase, in the second – the binding of bilirubin to albumin is disrupted when prescribing the above drugs.

Clinic: jaundice increases by the end of the first and the beginning of the second day after birth. Hepatosplenomegaly is not observed. Stools have a normal color. By the second week after birth, bilirubin can reach 342-513 mmol / l, and then gradually decreases. Discontinuation of breastfeeding for 1-2 days leads to a rapid decrease in bilirubin levels in the blood. With the resumption of breastfeeding, the level of bilirubin again gradually increases.

Jaundice during parenteral breastfeeding

Pathogenesis: under the influence of amino acids inhibits the excretion of bilirubin, this process is sharply enhanced by the use of fat emulsions.

Clinic: after a week of complete parenteral nutrition, signs of hepatocyte damage can be detected: increased serum activity of 5-nucleotidase, γ glutamyl-transpeptidase. Abolition of parenteral nutrition usually leads to a fairly rapid disappearance of jaundice and biochemical disorders.

METHODS OF CLINICAL EXAMINATION AND EVALUATION OF JAUNDICE

Skin color. Examination for the presence of jaundiced skin should be performed when the child is fully undressed, provided sufficient (optimally daylight). To do this, lightly press on the baby's skin to the level of the subcutaneous base.

Prevalence of jaundiced skin color. To assess the stages of jaundice and correlation with the level of bilirubin in the serum, it is advisable to use a modified Kramer scale (Fig. 1).

This figure shows that jaundice first appears on the face, then spreads to the child's limbs, reflecting the increase in serum bilirubin levels. Next to the figure are approximate indicators of bilirubin levels.

An alternative to using a visual assessment on the Kramer scale may be to determine the level of bilirubin in the skin by transcutaneous bilirubinometry (TCB). If the child's skin color is detected in zones 3-5, it is recommended to determine the total serum bilirubin (TSB) or TCB.

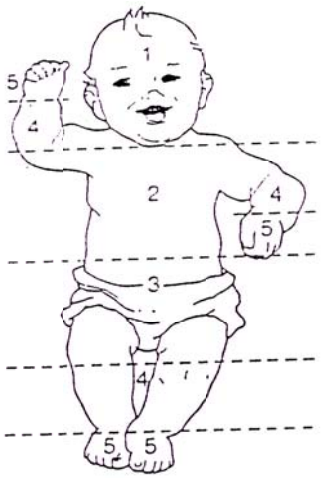

Fig.1 Stage of appearance of jaundiced skin color in newborns depending on the level of bilirubin

Table 2

Stages of jaundice in newborns depending on the level of bilirubin

Zone	1	2	3	4	5
TSB (μmol / l)	100	150	200	250	More 250

Time of jaundice and its severity. Jaundice, which appears in the first 24 hours of a child's life, is always a sign of pathology, so these newborns should start phototherapy immediately and at the same time determine the level of serum bilirubin. Also serious signs of danger are the spread of jaundice to zone 4 on the second day of life and to zone 5 after 48 hours (table 2).

Table 3

Criteria for "dangerous" jaundice of the newborn
(WHO, 2003 ISBN 92 4 154622 0) (ВОО3, 2003 ISBN 92 4 154622 0)

Child's age (hours)	Localization of jaundice	Conclusion
24	Any localization	"Dangerous" jaundice
24-48	Limbs	
> 48	Feet, hands	

If symptoms of "dangerous" jaundice appear, phototherapy should be started immediately, without waiting for the result of total serum bilirubin.

Risk factors affecting bilirubin levels and severity of jaundice. When assessing a newborn with jaundice, it is necessary to take into account various factors that may affect the increase in serum bilirubin:

- prematurity;
- hemorrhage (cephalohematoma, skin hemorrhage);
- malnutrition, frequent vomiting;
- a sharp decrease in body weight of the child;
- the presence of generalized infection;
- incompatibility of blood of mother and child by group and rhesus factor;
- hereditary hemolytic anemia or hemolytic disease

It is also important to assess the risk factors for acute lesions of the central nervous system (*bilirubin encephalopathy*):

- neonatal asphyxia;
- acidosis;
- prematurity;
- acute hemolysis;
- inadequate therapy of neonatal jaundice or its absence;
- hypoalbuminemia.

Clinical condition of the newborn. If jaundice occurs, the child's clinical condition should be assessed:

- the degree of adequacy of the child, the activity of reflexes;
- adequacy of breastfeeding (at least 8 times a day);
- condition of skin turgor and moisture of mucous membranes;
- the size of the liver and spleen;
- frequency of urination and nature of urine;

In newborns with jaundice, it is extremely important to monitor the appearance of symptoms of bilirubin encephalopathy, indicating acute damage to the central nervous system:

- the appearance of inhibition, drowsiness, lethargy and suppression of the sucking reflex in the early stages of the central nervous system;

- increased irritability, muscular hypertension, high-pitched cry, possible fever in a later period;

- in irreversible stages, the child has opisthotonus, convulsions, apnea, monotonous shrill cry, deep stupor or coma

SCOPE OF DIAGNOSTIC STUDIES

1. General blood test, counting the number of reticulocytes.
2. General analysis of urine.
3. Biochemical analysis of blood (level of bilirubin and its fractions, total protein and its fractions, transaminase activity, cholesterol level, bile acid levels, α-fetoprotein content);
4. Biochemical analysis of urine (determination of bilirubin and urobilinogen);
5. Coagulogram;
6. Direct Coombs test. Coombs' test is a test to detect antibodies attached to the surface of erythrocytes or dissolved in plasma.

Indirect Coombs' test detects anti-erythrocyte antibodies in blood plasma, performed before blood transfusion and during pregnancy. Coombs direct test - detects antibodies fixed on the surface of erythrocytes. Carried out on suspicion of autoimmune hemolytic anemia, hemolysis in autoimmune diseases, after taking drugs (methyldopa, penicillin, quinine), after blood transfusions and hemolytic dise

7. Determination of glucose-6-phosphate dehydrogenase activity of erythrocytes of the child;
8. PCR to detect rubella, cytomegalovirus, herpes viruses, toxoplasmosis in mother and child, HBgAg and antibodies to HB in mother and child.
9. Ultrasound and X-ray (if necessary) examination of the liver;
10. Consultation in the genetic center with appropriate tests in case of suspicion of congenital metabolic abnormalities.ase of newborns

ALGORITHM OF DIFFERENTIAL DIAGNOSIS OF NEONATAL JAUNDICE (WHO, 2003 ISBN 92 4 154622 0)

Table 4

№	Signs			Preliminary diagnosis
	Anamnesis	Clinical symptoms	Examination	
1	**Jaundice in the first 36 hours of a child's life:** Risk of ABO or Rh incompatibility between mother and child or G6FDG deficiency in the previous child; Familial cases of G6FDH deficiency, jaundice, anemia, liver enlargement, spleen removal	●**"Dangerous" jaundice** ● Pale skin and mucous membranes ● Generalized edema; ● Male (only in cases of confirmation of G6FDG deficiency)	**Hemoglobin <130 g / l** (hematocrit <40%); **Coombs' positive test:** ● Group ABO or Rh incompatibility between mother and child; ● Positive screening for G6FDG	**Hemolytic disease of the newborn** Take measures to prevent anemia and treat hemolytic jaundice
2	**Time of jaundice development with 2nd to 5th day**	**"Dangerous" jaundice Underweight baby** (birth weight <2500 grams or gestation <37 weeks)	No other causes of jaundice were identified	**Jaundice in a premature baby**
3	**Time of jaundice development with 2nd to 7th day**	●**"Dangerous" jaundice**	● **Sepsis** ● There is no confirmation of other causes of jaundice	**Jaundice associated with sepsis** Treat sepsis and conduct phototherapy (if necessary)
4	**The period of jaundice development is from the 2nd day and later**	● **"Dangerous" jaundice;**	● No confirmation of other causes of jaundice; ● Positive screening for G6FDG	**Jaundice associated with G6FDH deficiency** Treat as a hemolytic disease
5	**The time of development of encephalopathy from the 3rd to the 7th day** Late onset or no treatment for "dangerous" jaundice	● **"Dangerous" jaundice** ● Convulsions; ● Opisthotonus; ● The child is lethargic; ● Lethargy; ● Sluggish sucking	Coombs' positive test	**Bilirubin encephalopathy or nuclear jaundice**

The diagnosis cannot be confirmed in the absence of symptoms in bold. The presence of the above symptoms does not confirm the diagnosis. The diagnosis is confirmed in the presence of signs highlighted in italics. The presence of signs written in a simple font helps to confirm the diagnosis, but their absence does not preclude a diagnosis.

BASIC PRINCIPLES OF TREATMENT OF A NEWBORN WITH JAUNDICE

Newborn with the level of bilirubin of umbilical cord blood more than 50 µmol / l. Total serum bilirubin (TSB) should be re-determined no later than 4 hours after birth and an hourly increase in bilirubin levels should be calculated. In the future, it is recommended to conduct a laboratory examination depending on the clinical condition of the child.

Newborn with early or "dangerous" jaundice. Phototherapy should be started immediately. Simultaneously with the beginning of phototherapy to take a blood sample to determine TSB. If at the birth of a child its blood type, rhesus affiliation and direct Coombs' test were not determined, these studies should be performed. It is recommended to determine the level of hemoglobin, hematocrit, as well as counting the number of erythrocytes and reticulocytes. In the presence of clinical data indicating other diseases, additional examinations are performed in accordance with the relevant protocols.

Newborn with "physiological" jaundice.

Table 5

Newborn with uncomplicated "physiological" jaundice

The results of the clinical examination	*Examination and treatment*
Jaundice appears from the end of the second day, does not go below the umbilical line (zones 1-2 on the Cramer scale)	If possible – perform transcutaneous bilirubinometry Ensure adequate breastfeeding Provide further observation and care of the child, namely temperature, breastfeeding. In the absence of other contraindications, the child may be discharged home from the hospital on the third day under the supervision of a district pediatrician or family doctor, who, in turn, must examine the newborn on the 5th day of life.
The child is active, physiological reflexes, active sucking reflex, body temperature is normal	
The liver and spleen are not enlarged	
Urine is light, the number of urinations corresponds to the age of the child, stools are colored	

Table 6

Newborn with complicated "physiological" jaundice

The results of the clinical examination	*Examination and treatment*
Jaundice appears from the end of the second day and spreads to areas below the umbilical line and to the extremities (zones 3-4 on the Cramer scale)	**If the child is intact**: Determine total serum bilirubin Solve the question of starting phototherapy (if bilirubin 250 and above) Ensure adequate breastfeeding Provide further observation and care of the child **At the broken condition of the child**: Start phototherapy immediately Determine total serum bilirubin Ensure adequate breastfeeding Provide further observation and care of the child Provide detection and treatment of comorbidities
The child's condition may be disturbed in the form of lethargy, inhibition, impaired reflexes (including the sucking reflex)	
The liver and spleen may be enlarged	
Urine is light, the number of urinations corresponds to age, stools are colored	

Table 7

Newborn with prolonged and late jaundice

The results of the clinical examination	*Examination and treatment*
Jaundice remains more than 14 days in full-term and more than 21 days in premature without a clear tendency to decrease **Or** Jaundice appeared after 7 days of life	Determine total serum bilirubin and its fractions If the liver is enlarged, determine ALT and AST To control the weight of the newborn Assess the adequacy of breastfeeding Provide further examination for neonatal jaundice **Immediate hospitalization of the newborn in the following cases:** Deterioration of the child's condition Total serum bilirubin is more than 200 μmol / l Fraction of direct bilirubin more than 34 μmol / l (more than 20% of the level of BSA) Enlargement of the liver or spleen The presence of dark urine and / or discolored stools
The child's condition may be satisfactory or disturbed	
The liver and spleen may be enlarged	
There may be a change in the color of urine and feces	

In infants who are exclusively breastfed, jaundice may have two peaks of bilirubin increase (between 4-5 and 14-15 days). In such cases, there is a slow decrease in the intensity of jaundice, and jaundice may remain until 12 weeks of age. This jaundice is diagnosed by the method of exclusion in healthy full-term infants in the absence of general disorders. Such jaundice does not require drug therapy and cessation of breastfeeding.

Phototherapy

Methods of phototherapy for neonatal jaundice. Phototherapy is certainly the most effective method of reducing bilirubin in newborns with neonatal jaundice. Timely and correctly performed phototherapy reduces the need for replacement blood transfusion to 4% and reduces the likelihood of complications of neonatal jaundice.

Monitoring during phototherapy. It is necessary to assess the clinical condition of the newborn with jaundice at least 3 times a day. Keep in mind that:

- during phototherapy there is a rapid disappearance of bilirubin from the skin of the child, so the color of the skin does not reproduce the existing level of hyperbilirubinemia during phototherapy and within 24 hours after its termination;
- during phototherapy it is recommended to maintain the child's body temperature in the range of 36.5-37.5 C ° and to monitor it every three hours;
- it is necessary to control the child's weight at least once a day;
- continue breastfeeding on demand without a night break at least 8 times a day;
- laboratory control.

In case of early and / or "dangerous" jaundice, repeat the determination of total serum bilirubin in 4-6 hours after the start of phototherapy, then - depending on the result of TSB and the clinical condition of the child. Normally, phototherapy is accompanied by a decrease in total serum bilirubin by 20-35 μmol / l or a decrease in growth rate below the level that requires replacement transfusion within 4-6 hours from the start of phototherapy. Otherwise, consider the ineffectiveness of ongoing phototherapy and move on to intensive phototherapy or replacement blood transfusions.

In the case of complicated "physiological" jaundice or prolonged jaundice, the question of re-laboratory examination should be decided individually in each case, depending on the clinical condition of the child.

Duration and cessation of phototherapy. Phototherapy in a full-term newborn is stopped if the result of total serum bilirubin below the level indicated in Table 5 according to the age of the child and the presence or absence of risk factors.

Table 8

Criteria for discontinuation of phototherapy in full-term infants

total bilirubin level	hours of life
170	24
200	36
220	48
250	60
280	72 and older

Phototherapy in a premature newborn is stopped when the bilirubin result is below the level indicated in Table 9 according to the age of the child for at least 12 hours.

Table 9

Criteria for discontinuation of phototherapy in preterm infants

birth weight	total bilirubin level	hours of life
Up to 1000 gr	70	0-12
	100	24
	120	36
	130	48
	140	60
	150 and more	72 and older
1000-1500 gr	70	0-12
	120	24
	140	36
	150	48
	170	60
	200	72 and older

The issue of replacement blood transfusion is resolved in case of ineffective phototherapy, the development of the clinic of acute bilirubin encephalopathy or in the case of an increase in total serum bilirubin to critical levels.

FORECAST AND STATEMENT

In the case of a child's discharge on the 3rd day of life, it is necessary to examine the child at home before the child reaches 120 hours of age (5 days). In the uncomplicated course of "physiological" jaundice, the prevalence of jaundice of the skin below the umbilical line, good clinical condition of the child and well-established breastfeeding, the child may be discharged home under the supervision of a district pediatrician or family doctor.

With successful phototherapy, the issue of discharge of the child from the medical institution can be resolved no earlier than 24 hours after completion of phototherapy and in case of satisfactory clinical condition of the child, no increase in jaundice after discontinuation of phototherapy. The result of the last measurement of total serum bilirubin (TSB) should be noted on the nomogram.

If phototherapy has not been performed, but at the time of probable discharge jaundice of the skin spreads below the umbilical line, it is necessary to determine the concentration of total serum bilirubin and note the value on the nomogram.

If the TSB result is in a high-risk zone, or in a high-intermediate risk zone if the child has concomitant risk factors, there is a high probability of bilirubin levels exceeding the 95th percentile in the coming days, which may require treatment. In this case, the discharge should be postponed for at least 24 hours or the newborn should be transferred to the neonatology department.

If the result of TSB is in the low risk zone, the probability of further increase in hyperbilirubinemia is minimal.

If the result of the TSB is in the area of intermediate risk, the presence of concomitant risk factors should be taken into account and the issue of discharge should be decided individually.

Prior to the child's discharge from the medical institution, information on the child's care and monitoring must be provided to the mother or caregivers.

After discharge from the maternity hospital of a child with jaundice or when it appears after discharge:

- assess the location of jaundice, the general clinical condition of the child, the adequacy of feeding;
- in the presence of jaundiced skin of the child only up to the level of the umbilical line and in good clinical condition of the child should observe the child at home without mandatory laboratory examination.
- if jaundice spreads to the extremities (especially the palms and soles of zones 4-5 on the Kramer scale) and / or long-term storage of jaundice of these areas should ensure the referral of the child to a medical institution.

QUESTIONS FOR SELF-CONTROL

1. What is early, prolonged and late jaundice? How are they different from each other?
2. Types of jaundice with indirect hyperbilirubinemia
3. Types of jaundice with direct hyperbilirubinemia
4. What is jaundice during breastfeeding?
5. How to determine the level of hyperbilirubinemia by the spread of jaundiced skin?
6. What clinical and laboratory studies should be performed for the differential diagnosis of jaundice in newborns?
7. What is bilirubin encephalopathy?
8. What is phototherapy? How is it conducted?
9. When should phototherapy be stopped?
10. How to monitor a newborn with jaundice after discharge from the maternity hospital?

Tasks

Situational task 1. A boy of 5 weeks, born from III pregnancy, I pregnancy ended medical abortion, II - miscarriage. This pregnancy took place with toxicosis in the I and II halves. Childbirth - on time. Birth weight 3,200 g, length 51 cm, cried out immediately. In the first days of life, the child developed a jaundice, with a tendency to increase. In the mother, blood group A (II), rhesus-negative; the child has blood group A (II), rhesus-positive. 14 hours after birth, the boy had severe jaundice, the hourly increase in bilirubin was 7.14 μmol / l. A replacement blood transfusion was performed. In the future, the child's condition gradually improved, jaundice decreased. Discharged home on the 14th day of life; blood bilirubin 27.2 μmol / l, Hb 170 g / l.

During the examination at the station in the clinic at the age of 4 weeks, a satisfactory condition was noted, there was no jaundice. Hb 116 g / l, er. 3.4 million examination at the age of 5 weeks revealed: satisfactory condition, no jaundice, pronounced pallor of the skin, Hb 106 g / l, er. 3 million. 1) What is your diagnosis? 2. Prescribe treatment.

Correct answer: 1. Hemolytic disease of the newborn by rhesus factor, jaundice, moderate. Late anemia of the 1st degree of severity (hyporegenerative). 2) For the correction of anemia use recombinant erythropoietin alpha 200 IU / kg once every 3 days, subcutaneously, 4-6 weeks. Iron supplements orally 2–4 mg Fe / kg body weight once a day for 4–6 weeks.

Situational task 2. The boy was born from I pregnancy, I childbirth. Pregnancy and childbirth were uncomplicated, birth weight 3,200 g, length 52 cm. Maternal blood group 0 (I), rhesus-positive. Blood group of child A (II),

rhesus-positive. Apgar score 8/8 points. 15 hours after birth, the child developed jaundice of the first degree, the hourly increase in bilirubin was 9.5 mmol/L. Coombs' reaction is positive. Replacement blood transfusion operation were done.

On the 3rd day, the child's condition suddenly worsened, began to refuse feeding, belched. The jaundice of integuments which has got greenish coloring increased. The liver protruded from the edge of the costal arch by 3 cm, dense. Urine is intensely yellow, stains the diaper. There was a colorless stool. What is your diagnosis? What are your further tactics and treatments?

Correct answer: 1. Hemolytic disease of the newborn on the AB0 system, jaundice, moderate, cholestasis syndrome. 2.Replacement blood transfusion. Infusion therapy, phototherapy. Bilirubin level control. Correction of anemia. To monitor the cholestasis syndrome: ultrasound control of the liver and biliary tract, the level of total, direct and indirect bilirubin, analysis of urine and feces for bile pigments. In therapy: ursofalk 1-2 months, vitamin E.

Tests

1.A neonate was born from the 1st gestation on term. The jaundice was revealed on the 2nd day of life, then it became more acute. The adynamia, vomiting and hepatomegaly were observed. Indirect bilirubin level was 275 mmol/L, direct bilirubin level – 5 mmol/L, Hb- 150 g/L. Mother's blood group – 0(I), Rh+, childs blood group – A(II), Rh+. What is the most probable diagnosis?

a. Physiological jaundice
b. Hemolytic disease of the neonate (Rh-incompatibility)
c. Jaundice due to conjugation disorder
d. Hepatitis
e. Hemolytic disease of the neonate (AB0 incompatibility), icteric type

2. A woman delivered a child. It was her fifth pregnancy but the first delivery. Mothers blood group is A(II)Rh-, newborns – A(II)Rh+. The level of indirect bilirubin in umbilical blood was 58 mkmol/L, haemoglobin – 140 g/L, RBC – $3{,}8\times10^{12}$/L. In 2 hours, the level of indirect bilirubin turned 82 mkmol/L. The hemolytic disease of newborn (icteric-anemic type, Rh-incompatibility) was diagnosed. Choose the therapeutic tactics:

a. Symptomatic therapy
b. Antibiotics
c. Conservative therapy
d. Blood transfusion (conservative therapy)
e. Replacement blood transfusion (conservative therapy)

3.A baby was born at 36 weeks of gestation. Delivery was normal, by natural way. The baby has a large cephalohematoma. The results of blood count are: Hb – 120g/L, Er – $3,5\times10^{12}$/L, total serum bilirubin – 123 mmol/lL, direct bilirubin – 11 mmol/L, indirect – 112 mmol/L. What are causes of hyperbilirubinemia in this case?

a. Erythrocyte hemolysis
b. Disturbance of the conjugative function of liver
c. Mechanical obstruction of the bile outflow
d. Bile condensing
e. Intravascular hemolysis

4. Full term newborn has developed jaundice at 10 hours of age. Hemolytic disease of newborn due to Rh-incompatibility was diagnosed. 2 hours later the infant has indirect serum bilirubin level increasing up to 14 mmol/L. What is most appropriate for treatment of hyperbilirubinemia in this infant?

a. Phenobarbital
b. Phototherapy
c. Exchange blood transfusion
d. Intestinal sorbents
e. Infusion therapy

5. A newborn aged 3 days with hyperbilirubinemia (428 mkmol/L) developed following disorders. From beginning there were severe jaundice with poor suckling, hypotomia and hypodynamia. Little bit later periodical excitation, neonatal convulsions and neonatal primitive reflexes loss are noted. Now physical examination reveals convergent squint, rotatory nystagmus and setting sun eye sign. How to explain this condition?

a. Hydrocephalus
b. Spastic cerebral palsy
c. Skull injury
d. Brain tumor
e. Encephalopathy due to hyperbilirubinemia

6. A neonate was born from the 1st gestation on term. The jaundice was revealed on the 2nd day of life, then it became more acute. The adynamia, vomiting and hepatomegaly were observed. Indirect bilirubin level was 285 mmol/L, direct bilirubin level – 6 mmol/L, Hb- 145 g/L. Mothers blood group – 0(I), Rh+, childs blood group – A(II), Rh+. What is the most probable diagnosis?

a. Hemolytic disease of the neonate (Rh-incompatibility)
b. Hemolytic disease of the neonate (AB0-incompatibility), icteric type
c. Hepatitis

d. Jaundice due to conjugation disorder
e. Physiological jaundice

7. A baby boy was born in time, it was his mother 1st pregnancy. The jaundice was revealed on the 2nd day of life, then it progressed. The adynamia, vomiting and hepatomegaly were presented. The indirect bilirubin level was 275 mkmol/L, the direct bilirubin level – 5 mkmol/L, Hb- 150 g/L. Mothers blood group – 0(I), Rh+, child's blood group - A(II), Rh+. Make a diagnosis.

a. Hepatitis
b. Jaundice due to conjugation disorder
c. Hemolytic disease of newborn (ABO incompatibility), icteric type
d. Physiological jaundice
e. Hemolytic disease of newborn (Rh-incompatibility)

8. A child from the first non-complicated pregnancy but complicated labor had cephalhematoma. On the second day there developed jaundice. On the 3th day appeared changes of neurologic status: nystagmus, Graefes sign. Urea is yellow, feces- golden-yellow. Mothers blood group is A(II)Rh-, child- A(II)Rh+. On the third day childs Hb – 200 g/L, RBC– $6{,}1\times10^{12}$/L, bilirubin in blood – 58 mkmol/L due to unconjugated bilirubin, Ht – 0,57. What is the child's jaundice explanation?

a. Physiologic jaundice
b. Bile ducts atresia
c. Fetal hepatitis
d. Brain delivery trauma
e. Hemolytic disease of newborn

9. A full-term baby (the 1st uncomplicated pregnancy, difficult labour) had a cephalogematoma. On the 2nd day there was jaundice, on the third the following changes in neurological status appeared: nystagmus, Graefe syndrome. Urine was yellow, feces were of golden-yellow colour. Mothers blood group is A(II)Rh-, the babys one - A(II)Rh+. On the third day the childs Hb was 200g/L, RBCs - $6{,}1\times10^{12}$/L, blood bilirubin - 58 mkmol/L at the expense of unbound fraction. What caused the jaundice in the child?

a. Biliary atresia
b. Fetal hepatitis
c. Physiological jaundice
d. Neonatal anaemia
e. Craniocerebral birth trauma

10. On the 1st day of life a full-term girl (2nd labour) weighing 3500g, with Apgar score of 8 points, presented with jaundice. Indirect bilirubin of

blood – was 80 mkmol/L, 6 hours later – 160 mkmol/L. What is the optimal method of treatment?

a. Exchange blood transfusion
b. Infusion therapy
c. Enterosorbents
d. Phenobarbital treatment
e. Phototherapy

Correct answers: 1– e, 2 – e, 3 – a, 4 – c, 5 – e, 6 – b, 7 – c, 8 – d, 9 – e, 10 – a.

REFERENCE

Main sources:

1. Nelson textbook of Pediatrics 19th ed. / Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Philadelphia, Pa: Saunders Elsevier; 2011. – 2615 p.
2. Pediatrics. Textbook / O.B. Tiazhka, TV Pochinok, AN Antoshkina et al. / edited by O. Tiazhka - Vinnisa: Nova Knyha Publishers, 2011. – 584 p.
3. Order of the Ministry of Health № 255 of 27.04.2006 on approval of the clinical protocol for the provision of neonatological care to children "Jaundice of newborns" as amended in accordance with the Order of 08.06.2007 № 310.
4. Shabalov NP Neonatology / NP Shabalov. – Saint-Petersburg: Spec. Literature, 2006. – Vol. 1–2.
5. Yashchenko Yu. B. Neonatology: a textbook / Yu. B. Yashchenko, LV Kolyubakina, RO Moiseenko. – Kyiv, 2010.
6. Medline information retrieval database (http://www.ncbi.nlm.nin.gov/pubmed).

Additional sources:

1. Shadrin OG Ways to optimize the treatment of prolonged conjugative jaundice in infants / OG Shadrin, NF Chernega // Child health. – 2015. – № 6 (66). – S. 19–22.
2. Belousov Yu. V. Cholestasis syndrome in children / Yu. V. Belousov // Health of Ukraine. – 2011. – № 17 (270). – S. 52–54.
3. Klimenko TM Experience of application of ursodeoxycholic acid in newborns with cholestasis / TM Klimenko, O. Yu. Karapetyan, O. S. Karatay // Modern pediatrics. – 2012. – № 6 (46). – p. 90–92.