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Department of Internal Medicine № 2

Jaundice Syndrome

Methodical materials
the main professional educational program of higher education - a program of a specialist in a specialty
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Vladikavkaz

Methodological materials are intended for teaching 4th year students (7.8 semesters) of the Faculty of Medicine of the Federal State Budgetary Educational Institution of Higher Education SOGMA of the Ministry of Health of the Russian Federation on the discipline "Faculty therapy".

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Jaundice Is a polyetiological syndrome characterized by icteric staining of the skin and mucous membranes due to the accumulation of excess bilirubin in the tissues. At the same time, the level of bilirubin in the blood is increased. Jaundice is a clinical syndrome characteristic of a number of diseases of the internal organs. It is extremely important for a practicing physician to know the main causes of jaundice, features of the clinical course and diagnosis of various types of jaundice. Depending on the cause of the increase in the level of bilirubin in the blood, there are two main types of jaundice: true jaundice and false jaundice (pseudo jaundice).

Jaundice (true)- a symptom complex, characterized by icteric staining of the skin and mucous membranes, due to the accumulation of bilirubin in the tissues and blood. Depending on the causes of hyperbilirubinemia, hemolytic (suprahepatic), parenchymal (hepatic) and mechanical (subhepatic) jaundice are distinguished (Table 1).

Таблица 1. Классификация видов желтух

Вид желтухи	Основной патологический процесс	Ведущий механизм развития желтухи	Нозологические формы и синдромы
Надпеченочная	Повышенный распад эритроцитов	Повышенное образование билирубина, недостаточный захват его печенью	Гемолитическая желтуха, гематомы, инфаркты
Печеночная	Поражение гепатоцитов и холангиол	Нарушение экскреции и захвата билирубина, регургитация билирубина в кровь	Острый и хронический гепатит, цирроз печени. Холестатическая желтуха при первичном билиарном циррозе и поражении гепатоцитов
		Нарушения конъюгации и захвата билирубина	Желтуха новорожденных, энзимопатическая
Подпеченочная	Нарушение проходимости желчных протоков	Нарушение экскреции и регургитация билирубина в кровь	Нарушение нормального оттока желчи (камень, опухоль, паразиты, воспалительный экссудат)

False jaundice (pseudo-jaundice) is an icteric coloration of the skin (but not mucous membranes!) Due to the accumulation of carotenes in it during prolonged and abundant consumption of carrots, oranges, pumpkin, and also arising from the ingestion of acriquine, picric acid and some other drugs.

Parenchymal jaundice (hepatic)- true jaundice, which occurs with various lesions of the liver parenchyma. It develops as a result of infectious or toxic damage to hepatocytes and disruption or complete cessation of their functioning. It is caused by disorders of metabolism, transport and uptake of bilirubin in hepatocytes and bile ducts (cytolytic syndrome). Parenchymal jaundice also occurs when bile is retained in the smallest intrahepatic ducts (intrahepatic cholestasis), when the

clinical picture of obstructive jaundice develops, but there are no obstacles outside the liver. This condition is observed with some types of hepatitis, biliary cirrhosi

of the liver, as well as with drug intoxication. Bile pigments penetrate into the lymphatic vessels and blood capillaries between the affected and partially dying hepatocytes, their content in the blood increases. Most of this bilirubin gives a direct reaction and is excreted in the urine, staining it dark in color. Less than usual, the amount of bile pigments gets into the intestines, therefore, in most cases, the feces are light. Urobilinogen, synthesized in the intestine, is absorbed, but the affected hepatocytes are not able to break it down into bile pigments. Therefore, the amount of urobilinogen in blood and urine increases (Fig. 1).

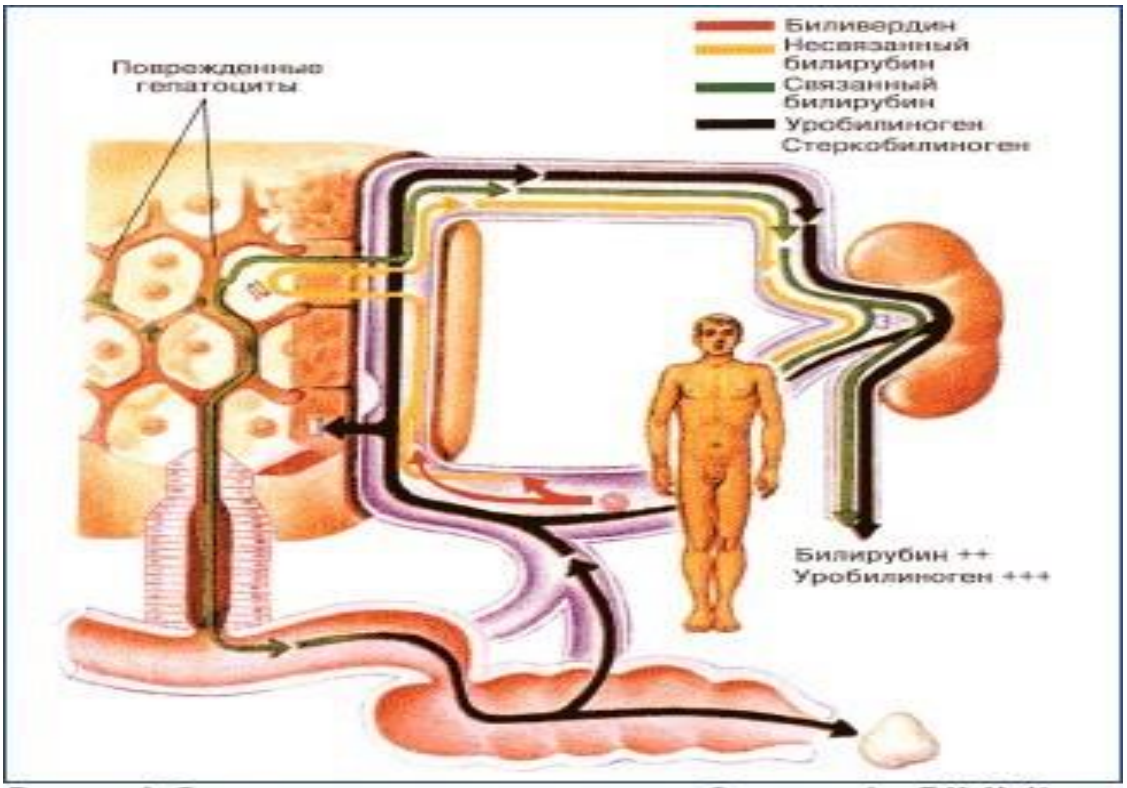

Рисунок 1. Схема патогенеза паренхиматозной желтухи (по F.H. Netter, 2001; С.Д. Подымовой, 2005)

In acute viral hepatitis, exposure to alcohol, drugs, chemicals, mushroom poisoning, sepsis, mononucleosis, leptospirosis, hemochromatosis, there is a prolonged complete obstruction of the bile ducts. The liver reacts to the effects of viruses, poisons, drugs with cytolytic or cholestatic syndrome.

Intrahepatic cholestasis develops with hepatitis of various etiologies: viral (viruses A, C, G, cytomegalovirus, Epstein-Barr virus), alcoholic, drug, autoimmune. In acute viral hepatitis, the prodromal period lasts 2-3 weeks and is manifested by a

gradual increase in jaundice (with a reddish tint) against the background of weakness, fatigue, decreased appetite, nausea, vomiting, and abdominal pain.

The liver is affected by various drugs: psychotropic (chlorpromazine, diazepam), antibacterial (erythromycin, nitrofurans, sulfanilamide), antidepressants (carbamazepine), hypoglycemic (chlorpropamide, tolbutamide), antiarrhythmic (aymalin), anti-arrhythmic agents (aymalin), immunosuppressants Aminosuppressants When you stop taking the drug, recovery can be long - up to several months or even years; in some cases, liver damage progresses with the development of cirrhosis (nitrofurans). Intrahepatic cholestasis is observed in amyloidosis, thrombosis of the hepatic veins, congestive and shock liver.

Due to the defeat of hepatocytes, their function of capturing free (indirect) bilirubin from the blood, binding it with glucuronic acid to form non-toxic water-soluble bilirubin-glucuronide (direct) and releasing the latter into the bile capillaries decreases. As a result, the content of bilirubin in the blood serum increases (up to 50-200 μmol / l, rarely more). However, in the blood, not only the content of free, but also bound bilirubin (bilirubin-glucuronide) increases due to its reverse diffusion from the bile capillaries into the blood vessels during dystrophy and necrobiosis of hepatic cells. There is an icteric staining of the skin, mucous membranes.

The clinic of parenchymal jaundice is largely determined by its etiology. Parenchymal jaundice is characterized by a saffron-yellow, reddish skin color ("red jaundice"). At first, an icteric color appears on the sclera and soft palate, then the skin is colored. Parenchymal jaundice is accompanied by itching of the skin, but less pronounced than mechanical jaundice, since the affected liver produces less bile acids, the accumulation of which in the blood and tissues causes this symptom. With a prolonged course of parenchymal jaundice, the skin can acquire, as with mechanical jaundice, a greenish tint (due to the transformation of bilirubin deposited in the skin into biliverdin, which has a green color). Usually, the activity of aldolase, aminotransferases, especially alanine aminotransferase, increases in

the blood, other liver tests are changed. The urine becomes dark (beer-colored) due to the appearance of bound bilirubin and urobilin in it. Feces brighten or discolor due to a decrease in the content of stercobilin in it. The ratio of the amount of stercobilin excreted in feces and urobilin bodies in urine (an important laboratory criterion for differentiating the types of jaundice), which is normally 10: 1–20: 1, in hepatocellular jaundice is significantly reduced, reaching 1: 1 in severe lesions.

Pathological processes in the liver are often accompanied by a decrease in the flow of bile into the duodenum due to a violation of its formation, excretion and / or excretion. The liver is enlarged, painful on palpation. Hemorrhagic syndrome and mesenchymal inflammation syndrome are often observed. The presence of the latter indicates the sensitization of immunocompetent cells and the activity of the reticulohisthiolymphocytic system. It manifests itself as hyperthermia, polyarthralgia, splenomegaly, lymphadenopathy, and erythema nodosum.

The course depends on the nature of the liver damage and the duration of the action of the damaging principle; in severe cases, liver failure may occur. The final diagnosis of viral hepatitis is based on serological and immunological studies.

Mechanical (subhepatic, obstructive) jaundicedevelops as a result of partial or complete obstruction of the biliary tract with impaired passage of bile into the intestine. The cause of the obstruction may be calculi of the common bile duct; cancer, cyst, abscess in the head of the pancreas; stenosis, swelling of the large papilla or bile ducts (metastases), their post-traumatic strictures (after surgery, colic with discharge of stones) and infection (parasites).

An obstruction in the biliary tract reduces the flow of bile through the tubules, hepatic excretion of water and / or organic anions. The pressure rises proximally from the obstruction site, and bile components from the intercellular spaces directly enter the blood. Bile accumulates in hepatocytes and bile ducts, and bile acids, lipids, bilirubin - in the blood. In the blood plasma, the content of bilirubin increases, giving a direct reaction. It is excreted in the urine and stains it dark

brown (the color of beer). There is no bile in the intestines, the feces are discolored. The formation of urobilinogen in the intestine does not occur, therefore it is absent in urine (Fig. 2). Bile acids can also enter the blood, the content of cholesterol and alkaline phosphatase increases in the plasma. Long-term cholestasis (for months and years) leads to the development of biliary cirrhosis of the liver.

A number of energy-dependent transport processes are involved in the formation of bile: the capture of bile acids, organic and inorganic ions, their transfer through the sinusoidal membrane into the hepatocyte and through the tubular membrane into the bile capillary.

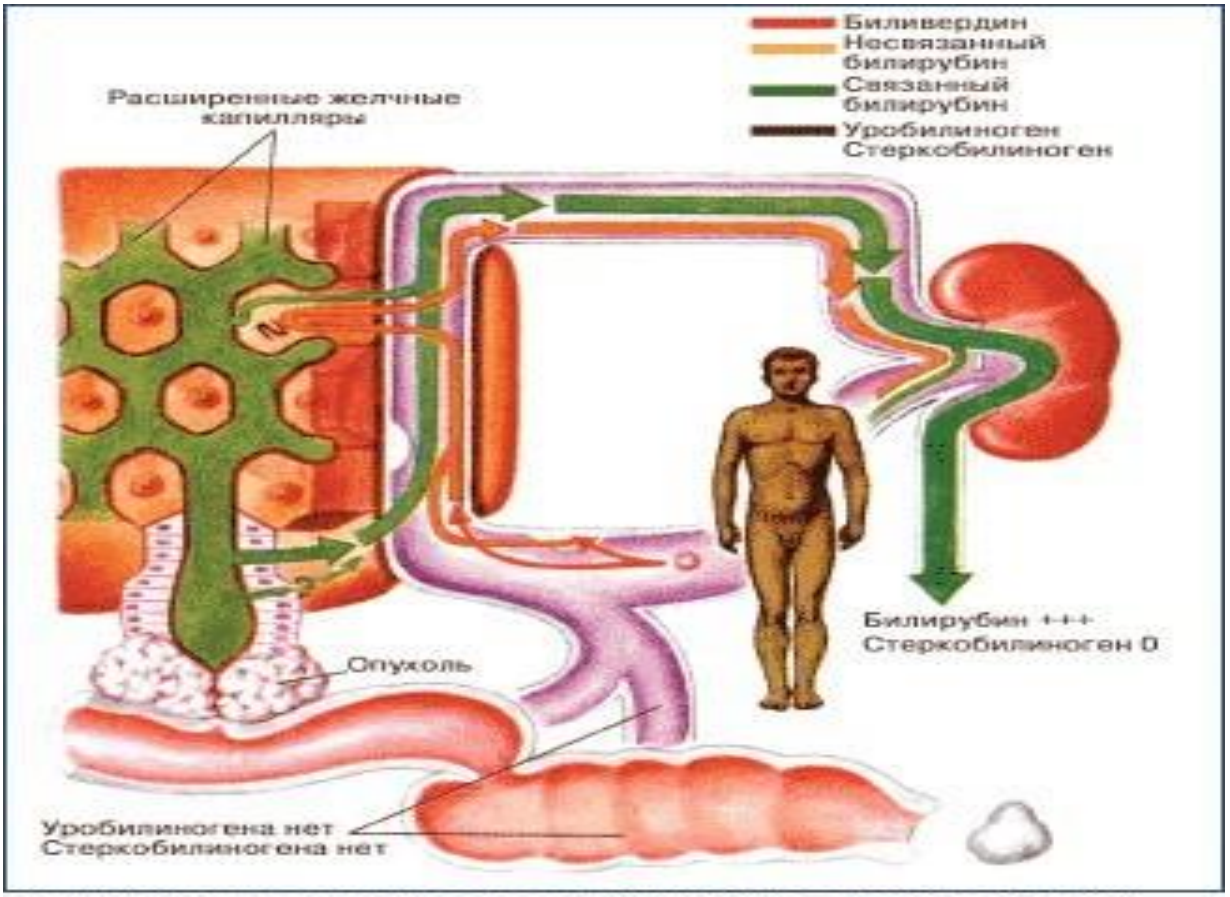

Рисунок 2. Схема патогенеза подпеченочной желтухи (по F.H. Netter, 2001; С.Д. Подымовой, 2005)

The transport of bile components depends on the normal functioning of carrier proteins built into both membranes (including Na + -K + -ATPase, carriers for bile acids, organic anions). At the cellular level, most often there is a violation of the synthesis of Na + -K + -ATPase and transport proteins or their function under the

influence of bile acids, inflammatory mediators (cytokines - tumor necrosis factor, interleukin-1b, etc.), endotoxins, drugs, changes in lipid composition , permeability of membranes, cell structures and tubules. Mechanical obstruction of the main ducts increases the pressure in the bile ducts, and hypertension suppresses the secretion of bile.

The accumulation of bile acids with pronounced surface-active properties causes damage to hepatocytes and an increase in cholestasis. The toxicity of bile acids depends on the degree of their lipophilicity and hydrophobicity. Hepatotoxic includes chenodeoxycholic (primary bile acid synthesized in the liver from cholesterol), as well as lithocholic and deoxycholic (secondary acids formed in the intestine from primary ones under the action of bacteria). The main link in the development of hepatocyte necrosis is considered to be damage under the influence of bile acids of mitochondrial membranes, a decrease in ATP synthesis in the cell, an increase in the intracellular concentration of Ca2 +, and stimulation of calcium-dependent hydrolases. Bile acids cause hepatocyte apoptosis - programmed cell death. Obstructive jaundice may be partial.

The clinical picture is determined by the duration of extrahepatic cholestasis. It manifests itself as jaundice, acholic feces, itching of the skin, impaired absorption of fats, steatorrhea, weight loss, hypovitaminosis A, D, E, K, xanthomas, skin hyperpigmentation, cholelithiasis, the formation of biliary cirrhosis of the liver (portal hypertension, liver failure). Itching of the skin, jaundice are observed with a significant violation of the excretory function of hepatocytes (more than 80%) and are not always early signs of cholestasis. Itching significantly impairs the quality of life of patients. Its nature is not completely clear. Probably, the compounds that cause itching are synthesized in the liver (this is evidenced by the disappearance of itching in the terminal stage of liver failure). Traditionally, itching of the skin is associated with the retention of bile acids in the skin and irritation of the nerve endings of the dermis, epidermis. There is no direct relationship between the severity of itching and the level of bile acids in serum.

Deficiency of bile acids in the intestine leads to impaired absorption of fats, promotes steatorrhea, weight loss, and a deficiency of fat-soluble vitamins (A, D, K, E). The severity of steatorrhea corresponds to the level of jaundice. Stool color is a reliable indicator of the degree of biliary obstruction (complete, intermittent, resolving). Vitamin D deficiency is one of the links of osteoporosis and osteomalacia (in chronic cholestasis), manifested by severe pain in the thoracic or lumbar spine, spontaneous fractures, especially ribs, with minimal trauma, and compression fractures of the vertebral bodies. Bone tissue pathology is aggravated by impaired absorption of Ca2 + in the intestine. Deficiency of vitamin K (necessary for the synthesis of coagulation factors in the liver) is manifested by hemorrhagic syndrome and hypoprothrombinemia, quickly relieved by parenteral administration of vitamin K. Clinical manifestations of vitamin E deficiency (cerebellar ataxia, peripheral polyneuropathy, retinal degeneration) are observed mainly in children. In adult patients, the content of vitamin E is always reduced, but there are no specific neurological symptoms. When the liver stores of vitamin A are depleted, dark adaptation disorders (night blindness) can develop. Long-term cholestasis promotes the formation of calculi in the biliary tract. In the presence of stones or after operations on the bile ducts, especially in patients with hepatic-intestinal anastomoses, bacterial cholangitis often joins (the classic Charcot triad: pain in the right hypochondrium, fever with chills, jaundice). peripheral polyneuropathy, retinal degeneration) are observed mainly in children. In adult patients, the content of vitamin E is always reduced, but there are no specific neurological symptoms. When the liver stores of vitamin A are depleted, dark adaptation disorders (night blindness) can develop. Long-term cholestasis promotes the formation of calculi in the biliary tract. In the presence of stones or after operations on the bile ducts, especially in patients with hepatic-intestinal anastomoses, bacterial cholangitis often joins (the classic Charcot triad: pain in the right hypochondrium, fever with chills, jaundice). peripheral polyneuropathy, retinal degeneration) are observed mainly in children. In adult patients, the content of vitamin E is always reduced, but there are no specific neurological symptoms.

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In the blood plasma, the level of all components of bile increases, primarily bile acids. The concentration of bilirubin (conjugated) increases during the first 3 weeks, and then fluctuates, maintaining a tendency to increase. When cholestasis resolves, it decreases gradually, which is associated with the formation of bilialbumin (bilirubin associated with albumin). Target erythrocytes may appear in peripheral blood (due to the accumulation of cholesterol in membranes and an increase in cell surface area). In the terminal stage of liver damage, the cholesterol level in the blood decreases. The increase in the activity of transaminases, as a rule, is not as significant as markers of cholestasis (alkaline phosphatase, 5-nucleotidase, γ-glutamyl transpeptidase). At the same time, in acute obstruction of the main ducts, the activity of AsAT, ALT can be 10 times higher than the norm (as in acute hepatitis). Sometimes the activity of alkaline phosphatase can be normal or decreased due to the absence of cofactors of this enzyme (zinc, magnesium, B12).

The results of clinical and biochemical studies in intra- and extrahepatic cholestasis may be similar. Sometimes extrahepatic obstruction is mistaken for intrahepatic cholestasis and vice versa. In favor of mechanical obstruction with the development of biliary hypertension, abdominal pain (with calculi in the ducts, tumors), palpable gallbladder testify. Fever and chills are symptoms of cholangitis in patients with calculi in the bile ducts or strictures of the biliary tract. The density and tuberosity of the liver on palpation reflect far-reaching changes or tumor lesions of the liver (primary or metastatic). If an ultrasound examination reveals a characteristic sign of a mechanical blockade of the biliary tract - supra-stenotic dilatation of the bile ducts (biliary hypertension) - cholangiography is indicated. Endoscopic retrograde cholangiopancreatography is the method of choice. If this is not possible, percutaneous transhepatic cholangiography is used. Both methods allow simultaneous drainage of the biliary tract in case of obstruction, however, with the endoscopic approach, there is a lower incidence of complications. With endoscopic retrograde cholangiopancreatography, sphincterotomy (to remove calculi) is possible. The diagnosis of intrahepatic cholestasis can be confirmed by liver biopsy, which is performed only after excluding obstructive extrahepatic cholestasis (to avoid the development of biliary peritonitis). however, with the endoscopic approach, there is a lower incidence of complications. With endoscopic retrograde cholangiopancreatography, sphincterotomy (to remove calculi) is possible. The diagnosis of intrahepatic cholestasis can be confirmed by liver biopsy, which is performed only after excluding obstructive extrahepatic cholestasis (to avoid the development of biliary peritonitis). however, with the endoscopic approach, there is a lower incidence of complications. With endoscopic retrograde cholangiopancreatography, sphincterotomy (to remove calculi) is possible. The diagnosis of intrahepatic cholestasis can be confirmed by liver biopsy, which is performed only after excluding obstructive extrahepatic cholestasis (to avoid the development of biliary peritonitis).

Hemolytic (suprahepatic) jaundiceoccurs as a result of intense breakdown of red blood cells and excessive production of indirect bilirubin. These phenomena occur

with hyperfunction of the cells of the reticuloendothelial system (primarily the spleen), with primary and secondary hypersplenism. Various hemolytic anemias, including congenital (microspherocytosis, etc.), can serve as a typical example of hemolytic jaundice. In this case, the formation of indirect bilirubin is so great that the liver does not have time to convert it into bound (direct) bilirubin. The causes of hemolytic jaundice can also be various other factors leading to hemolysis: hemolytic poisons, absorption of decay products of extensive hematomas into the blood, etc.

In practice, it is easier to diagnose hemolytic jaundice than others. With hemolytic jaundice, the skin acquires a lemon-yellow color, jaundice is moderately expressed, there is no itching. With severe anemia, pallor of the skin and mucous membranes is determined against the background of existing jaundice. The liver is normal in size or slightly enlarged. The spleen is moderately enlarged. In some types of secondary hypersplenism, severe splenomegaly can be detected. The urine is dark in color due to the increased concentration of urobilinogen and stercobilinogen. The reaction of urine to bilirubin is negative. The feces are intensely dark brown in color, the concentration of stercobilin in it is sharply increased. In blood tests - an increase in the level of indirect bilirubin, the concentration of direct biliburin is not increased (Fig. 3). Anemia, as a rule, is moderately expressed, reticulocytosis. ESR is slightly increased. Liver function tests, blood cholesterol within normal limits. Serum iron levels in the blood are elevated.

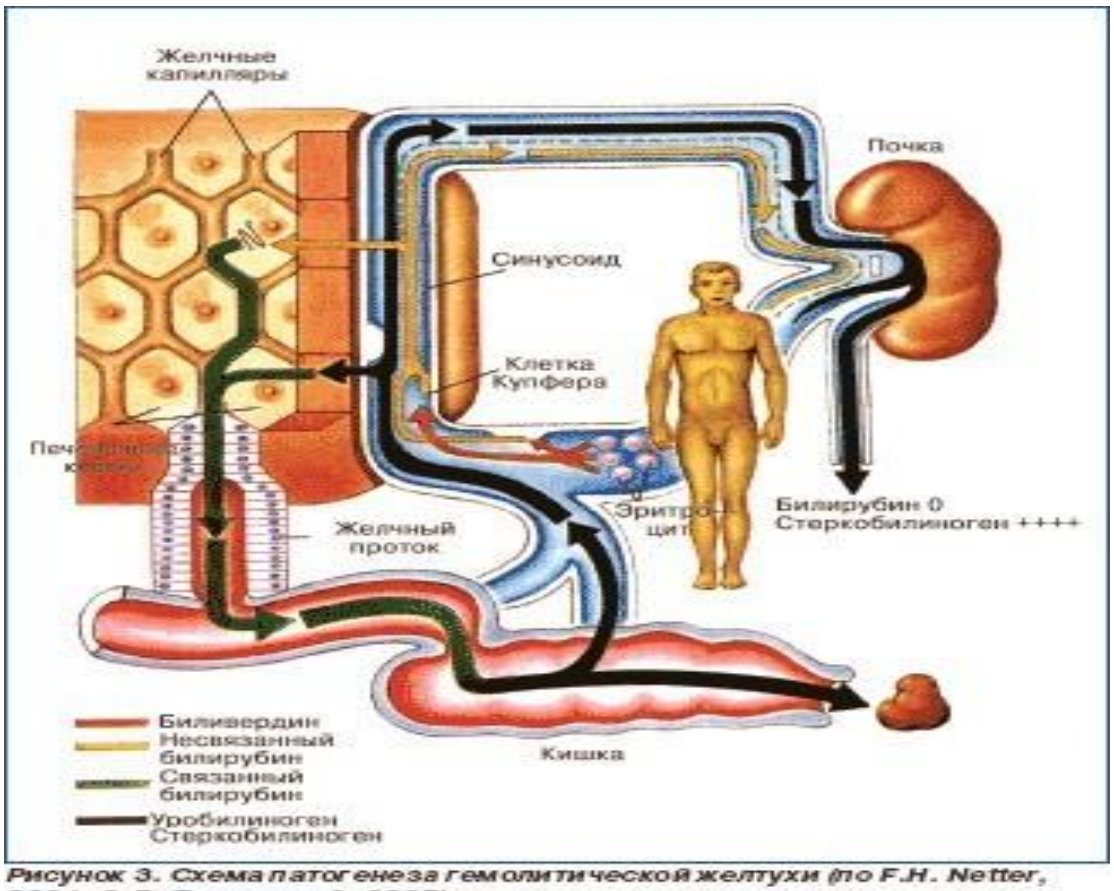

Рисунок 3. Схема патогенеза гемолитической желтухи (по F.H. Netter, 2001; С.Д. Подымовой, 2005)

Immune hemolytic anemias develop under the influence of antibodies on red blood cells. The main forms of immune hemolytic anemias: 1) autoimmune, caused by the appearance in the body of antibodies against its own erythrocytes; 2) hapten, caused by fixation on erythrocytes of antigens alien to the body - haptens (drugs, viruses, etc.) with antibodies formed in response to the combination of a hapten with a protein of the body; 3) isoimmune, associated with the ingestion of the mother's antibodies directed against the erythrocytes of the child into the body of the newborn (with incompatibility between the child and the mother for the Rh factor and much less often for the antigens of the AB0 system).

Autoimmune hemolytic anemias. The pathological process is based on a breakdown of immunological tolerance to its own erythrocytes. The clinical picture of the disease consists of signs of anemic syndrome; the severity of the patient's condition is determined by the severity and severity of the development of anemia. In a chronic, slowly developing process, the first sign of the disease may be mild jaundice (due to indirect bilirubin); anemia is also detected at the same time. In

other cases, the onset of the disease is characterized by violent hemolysis with rapidly growing anemia and jaundice. Body temperature often rises. The spleen is often enlarged. Perhaps an increase in the liver due to cholelithiasis, fatty degeneration. Usually, a functional systolic murmur is heard at the apex and at the base of the heart, a bifurcation of the II tone is often determined.

The blood picture is characterized by normochromic anemia (with acute hemolysis, the hemoglobin level can fall to catastrophic numbers, the patient can fall into an anemic coma). The morphology of erythrocytes does not change significantly, but sometimes their microspherocytosis is noted, which requires differentiation from hereditary microspherocytosis. In acute hemolysis, single erythrokaryocytes can be detected in the blood. The reticulocyte count is high. White blood does not change significantly, but the hemolytic crisis may be accompanied by a short-term neutrophilic leukocytosis (the appointment of steroid hormones during hemolysis may be accompanied by a very high neutrophilic leukemia with a shift to promyelocytes). The platelet count is usually normal. The bone marrow in autoimmune hemolytic anemia is characterized by irritation of the red sprout. Biochemical studies reveal, in addition to hyperbilirubinemia, an increase in the content of gamma globulins. With severe hemolysis, thrombosis in the mesenteric vascular system is possible with the appearance of severe paroxysmal pain and bloating due to intestinal paresis. As a rule, small vessels are thrombosed and intestinal gangrene does not develop, there is no need for surgical intervention. Intravascular hemolysis in response to cooling (cold hemoglobinuria) may occasionally occur. This form of hemolytic anemia is associated with the action of blood serum hemolysins on the patient's erythrocytes. small vessels are thrombosed and intestinal gangrene does not develop, there is no need for surgical intervention. Intravascular hemolysis in response to cooling (cold hemoglobinuria) may occasionally occur. This form of hemolytic anemia is associated with the action of blood serum hemolysins on the patient's erythrocytes. small vessels are thrombosed and intestinal gangrene does not develop, there is no need for surgical intervention. Intravascular hemolysis in response to cooling (cold hemoglobinuria)

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The diagnosis of autoimmune hemolytic anemia is established on the basis of general signs of hemolysis (an increase in the level of bilirubin in the blood or the appearance of hemosiderin in the urine, an increase in the percentage of reticulocytes in the blood and the detection of autoantibodies on the surface of erythrocytes using the Coombs test, which is positive in almost 60% of cases of autoimmune hemolysis).

Criteria for differential diagnosis of the main types of jaundiceare presented in table. 2.

Таблица 2. Дифференциально-диагностические лабораторные показатели при желтухах различного генеза

Лабораторные показатели	Надпеченочная желтуха	Печеночная желтуха (печеночно-клеточная)	Подпеченочная желтуха
Билирубин плазмы	Повышен за счет неконъюгированной фракции	Повышен преимущественно за счёт конъюгированной фракции	Повышен за счет конъюгированной фракции
Ферменты плазмы	Повышены значительно — ЛДГ, умеренно — АсАТ	Повышены значительно АлАТ и АсАТ	Повышены значительно ЩФ и ГГТП, может повышаться АлАТ
Билирубин в моче	Отсутствует	Значительно повышен	Значительно повышен
Уробилиноген мочи	Повышен	Отсутствует	Отсутствует
Периферическая кровь	Анемия, ретикулоцитоз, ускоренное СОЭ	Лейкопения, относительный лимфоцитоз, замедленное СОЭ	Лейкоцитоз нейтрофильного характера и ускоренное СОЭ
Маркеры вирусов гепатита	Отсутствуют	Положительные	Отсутствуют
Протромбин плазмы	Норма	Норма или снижен при тяжелом течении гепатита	Норма
Онкомаркеры	Отсутствуют	Отсутствуют	α-фетопротеин, РЭА повышены при опухолевой окклюзии желчных путей

Примечания: ЛДГ — лактатдегидрогеназа; АлАТ — аланинаминотрансаминаза; АсАТ — аспартатаминотрансаминаза; ГГТП — γ-глутамилтранспептидаза; ЩФ — щелочная фосфатаза; РЭА — раковоэмбриональный антиген.

Benign (functional) hyperbilirubinemia (pigmentary hepatosis) - diseases associated with hereditary disorders of bilirubin metabolism (enzymopathies), manifested by chronic or intermittent jaundice without pronounced primary

changes in the structure and function of the liver and without obvious signs of hemolysis and cholestasis

Crigler-Nayyar syndromedescribed in 1952 by American pediatricians JF Crigler and VA Najjar. The type of inheritance is autosomal recessive. At the molecular level, the defect is localized in one of 5 exons (1A – 5) of the gene for uridine diphosphate glucuronyl transferase (UDPGT) 1 * 1. It occurs with equal frequency in boys and girls. Pathogenesis - the absence (type 1 - Fig. 4) or decrease (type 2) the activity of UDPGT.

In Crigler-Nayyar syndrome type 1, unconjugated bilirubin in the blood is above 200 μmol / L. There is an accumulation of bilirubin in the nuclei of the gray matter of the brain, as a result of which convulsions, opisthotonus, nystagmus, athetosis, etc. develop. Manifestation occurs in the first hours of life, and patients more often die during the first year of life from nuclear jaundice. Liver changes (biochemical, histological) are not detected. The test with phenobarbital does not give a result (phenobarbital induces the activity of UDPGT, but due to the absence of this enzyme, the drug has no point of application).

Рисунок 4. Патогенез синдрома Криглера — Найяра 1-го типа

With Crigler-Nayyar syndrome type 2, manifestation occurs somewhat later - in the first months of life. The manifestations are similar to type 1 syndrome, but less

severe, since UDFGT is present in hepatocytes, although its activity is significantly reduced. The level of unconjugated bilirubin in the blood does not reach 200 μmol / L.

Dabin-Johnson syndromedescribed in 1954 by TN Dubin and GD Johnson. The type of inheritance is autosomal dominant. The frequency is 0.2–1.0%. Clinical manifestations usually develop in men 20-30 years old. The pathogenesis consists in the failure of the ATP-dependent transport system of hepatocytes (tubules), as a result of which the transport of bilirubin into bile deteriorates and even its reflux from hepatocytes into the blood develops (Fig. 5).

Рисунок 5. Патогенез синдрома Дабина — Джонсона

The clinic of the Dabin-Johnson syndrome is represented by constant jaundice without itching or (rarely) with slight itching, pain in the right hypochondrium with periodic aggravation like biliary colic, severe dyspeptic symptoms, fatigue, poor appetite, low-grade fever, hepatomegaly. Splenomegaly is also possible.

Diagnostics of the Dabin-Johnson syndrome is based on the detection of conjugated and unconjugated (due to deconjugation and reflux of bilirubin into the blood) hyperbilirubinemia in the blood up to 100 μmol / l, in the urine - bilirubinuria. Alkaline phosphatase values are usually unchanged. A rise in the level of bromsulfalein in the blood is characteristic 2 hours after administration.

With cholecystography, the shadow of the gallbladder is absent. Worsening, as a rule, occurs during pregnancy or taking oral contraceptives.

Macroscopically, dark spots ("chocolate liver") are determined in the liver tissue, the appearance of which is associated with a violation of the secretion of metabolites of tyrosine, tryptophan, phenylalanine. Microscopically, coarse grains of lipofuscin pigment are detected, which accumulate mainly in the center of the lobules.

Rotor Syndrome described in 1948 by AB Rotor, L. Manahan, A. Forentin. The type of inheritance is autosomal dominant. The pathogenesis is associated not only with a violation of the excretion of bilirubin (as in the Dabin-Johnson syndrome), but also with a violation of its capture by the sinusoidal pole of hepatocytes. It develops more often in boys during puberty. The clinic is similar to the Dabin-Johnson syndrome. In the blood, hyperbilirubinemia is determined up to 100 μmol / l (the indicators of direct and indirect bilirubin are equally increased). Bilirubinuria occurs; impaired absorption of bromsulfalein by the liver, but there is no second peak in blood concentration, as in Dabin-Johnson syndrome; with cholecystography, the gallbladder is contrasted. With liver biopsy, pigment accumulation is rarely detected, fine-droplet fatty degeneration is more characteristic, mainly along the bile capillaries.

Lucy-Driscoll Syndrome- a rare variant of hereditary hyperbilirubinemia. The disease manifests itself in children in the first days of life, but only in those who are breastfed. Severe hyperbilirubinemia develops, bilirubin encephalopathy is possible. Violation of bilirubin conjugation is due to the presence of an inhibitor of UDFGT in the mother's milk, therefore, the cessation of breastfeeding leads to recovery.

Aagenes syndrome(Norwegian cholestasis) is manifested by impaired liver function due to hypoplasia of its lymphatic vessels with the development of cholestasis. Manifestation usually occurs in the neonatal period, with possible

relapses in adults. Perhaps intermittent jaundice, accompanied by a deficiency of vitamin E, as a result of which degenerative changes in the central nervous system occur.

Beiler's Syndrome(malignant familial cholestasis) is an extremely rare variant of genetically determined hyperbilirubinemia. It develops in the first week of a child's life. In the pathogenesis, the formation of periportal fibrosis and the proliferation of the bile ducts are important, due to which cholestasis develops. The disease proceeds with severe jaundice (bilirubin in the blood reaches 300 μmol / l due to direct), hepato- and splenomegaly. The prognosis is poor.

Primary hyperbilirubinemia- a very rare disease associated with excessive formation of early-labeled bilirubin in the bone marrow. The cause is thought to be premature destruction of immature erythrocyte precursors in the bone marrow, i.e. ineffective erythropoiesis. In peripheral blood, destruction of red blood cells occurs at a normal rate. Clinically, the disease is manifested by compensated hemolysis.

Gilbert's syndrome described in 1901 by the French physicians A. Gilbert and P. Lereboullet.

Рисунок 6. Патогенез синдрома Жильбера

In Gilbert's syndrome, the seizure, transport and conjugation of bilirubin are impaired. There are (Fig. 6):

- deficiency of bilitranslocase, which is responsible for the capture of bilirubin from the blood and its transport to the hepatocyte;

- deficiency of Y- and Z-protein ligands (the enzyme glutathione-S-transferase), which are responsible for the transfer of bilirubin to microsomes;

- UDFGT deficiency, which ensures the transfer of glucuronic acid to bilirubin.

The genetic defect consists in the presence of an additional dinucleotide TA on the A (TA) 6TAA promoter region of the gene encoding UDPGT, i.e. a section A (TA) 7TAA is formed. The type of inheritance is autosomal dominant.

There is a congenital variant of Gilbert's syndrome, when clinical manifestations develop at the age of 12-30 years without previous acute viral hepatitis, and Gilbert's syndrome, the clinical manifestations of which are manifested after acute viral hepatitis. In this case, the so-called post-hepatitis hyperbilirubinemia occurs. Moreover, it may be associated not only with the initiation of clinical manifestations of a genetic defect (with true Gilbert's syndrome), but also with the development of chronic viral hepatitis. That is, patients with post-hepatitis hyperbilirubinemia require careful monitoring and differential diagnosis between Gilbert's syndrome and chronic viral hepatitis.

In Gilbert's syndrome, the ratio of men and women is 3-4: 1. A. Gilbert described a characteristic triad of clinical manifestations: "hepatic mask" (jaundice), xanthelasma of the eyelids, frequency of symptoms. Typically, increased jaundice after infections, emotional and physical stress, taking anabolic steroids, glucocorticoids, androgens, rifampicin, cimetidine, chloramphenicol, streptomycin, sodium salicylate, ampicillin, caffeine, ethinylestradiol, paracetamol, i.e. after taking those drugs, in the metabolism of which UDFGT is involved. In addition, jaundice may worsen after fasting and vomiting. Patients are sensitive to cold, they easily develop "goose bumps". Pigmentation of the face, age spots on the skin are

rarely found. Severity in the right hypochondrium, dyspeptic phenomena, asthenovegetative disorders are common. So, A.I. Shatikhin et al. (1997), when examining 7 patients, found that all patients had increased reactive and personal anxiety, poor health and decreased activity. An increase in the percentage of D sleep was found; vegetative indicators of night sleep and wakefulness did not differ. Such changes in the psychological sphere and the organization of night sleep, according to the authors, arose primarily in response to an increase in the content of unconjugated bilirubin due to its effect on the hypothalamus. An increase in the level of unconjugated bilirubin also led to biorhythmological shifts, a restructuring of the motivational sphere, accompanied by an increased level of anxiety, which contributed to the development of asthenic syndrome. that all patients showed increased reactive and personal anxiety, poor health and decreased activity. An increase in the percentage of D sleep was found; vegetative indicators of night sleep and wakefulness did not differ. Such changes in the psychological sphere and the organization of night sleep, according to the authors, arose primarily in response to an increase in the content of unconjugated bilirubin due to its effect on the hypothalamus. An increase in the level of unconjugated bilirubin also led to biorhythmological shifts, a restructuring of the motivational sphere, accompanied by an increased level of anxiety, which contributed to the development of asthenic syndrome. that all patients showed increased reactive and personal anxiety, poor health and decreased activity. An increase in the percentage of D sleep was found; vegetative indicators of night sleep and wakefulness did not differ. Such changes in the psychological sphere and the organization of night sleep, according to the authors, occurred primarily in response to an increase in the content of unconjugated bilirubin due to its effect on the hypothalamus. An increase in the level of unconjugated bilirubin also led to biorhythmological shifts, a restructuring of the motivational sphere, accompanied by an increased level of anxiety, which contributed to the development of asthenic syndrome. vegetative indicators of night sleep and wakefulness did not differ. Such changes in the psychological sphere and the organization of night sleep, according to the authors,

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In 20% of cases with Gilbert's syndrome, a moderate increase in the liver is found; in 30% of cases - cholecystitis, including calculous, cholangitis; in 42% of cases - dysfunction of the gallbladder and the sphincter of Oddi; in 12.5% of cases - chronic hepatitis of aclogolic, viral etiology, as well as reactive; in 7.4% of cases - fatty degeneration of the liver; in 0.7% of cases - liver hemangiomas.

According to M.A. Konovalova et al. (1999), with ultrasound cholecystography, normal gallbladder function is noted in 29.3%, hypermotor dyskinesia - in 20.7%, hypomotor dyskinesia - in 50% of cases. With multimodal duodenal intubation, the same authors stated the presence of biliary dyskinesia in patients in 88% of cases (with a predominance of hypomotor gallbladder dyskinesia in 51.7% of cases); dysfunction of the sphincter of Oddi - in 72.4% of cases (hypotension of the sphincter - 39.7% of cases, hypertonicity - in 34.5% of the examined). In 96% of patients, changes in the biochemical composition of bile, changes in indicators characterizing the lithogenicity of bile: a decrease in the chole-cholesterol coefficient and cholato-cholesterol index, an increase in the lithogenicity index were revealed. The authors believe

With Gilbert's syndrome, in 30% of cases, hemoglobin increased by more than 160 g / l, in 15% of patients, mild reticulocytosis is detected, in 12% - a decrease in the osmotic resistance of erythrocytes. An increase in the content of hemoglobin in the blood is associated with its excessive synthesis with an increased level of bilirubin in the blood and tissues. The question of the presence of latent hemolysis in Gilbert's syndrome (reticulocytosis, decreased osmotic resistance of erythrocytes) is the topic of many years of discussion. Hyperbilirubinemia does not exceed 80–100 μmol / L with a significant predominance of the indirect fraction. Perhaps a slight violation of the excretion of bromosulfalein, an increase in the blood content of the intestinal fraction of alkaline phosphatase. In some cases, Gilbert's syndrome is combined with Marfan, Ehlers - Danlos syndromes.

Special tests have also been developed for the diagnosis of Gilbert's syndrome. So, limiting the calorie content of food to 400 kcal / day or fasting for two days leads to an increase in the level of free bilirubin in the blood. Intravenous administration of 40 mg of niacin contributes to a decrease in the osmotic resistance of erythrocytes and an increase in the level of bilirubin in the blood. Taking phenobarbital 3 mg / kg / day for 5 days in Gilbert's syndrome initiates a decrease in the level of bilirubin in the blood, since the drug induces the activity of UDPGT. The rifampicin test is also used: after the administration of 900 mg of rifampicin in patients with Gilbert's syndrome, the level of bilirubin in the blood increases significantly. Morphologically, the accumulation of the dust-like golden-brown enzyme lipofuscin is characteristic mainly in the center of the lobules. The enhanced formation of lipofuscin is considered an adaptive mechanism, since this pigment is the result of the autooxidation reaction of metal flavoproteins and is one of the sources of energy in the hepatocyte. In addition, histological examination reveals concomitant liver pathologies of varying severity in 20–24% of patients.

Meilengracht syndromeuntil recently, it was considered almost synonymous with Gilbert's syndrome, which was often even called "Gilbert-Meilengracht syndrome." However, later it was proved that these are different syndromes with a

similar clinical picture. Common to the two syndromes are a decrease in the level of bilirubin when prescribing activators of microsomal liver enzymes, the age of manifestation, the intermittent nature of jaundice, the level of bilirubin in the blood no more than 80-100 μmol / L due to the unconjugated fraction, clinical manifestations in the form of icterus of the skin and mucous membranes, dyspepsia, asthenia. But with Meilengracht's syndrome, there is only an isolated decrease in the activity of UDPGT, and the hepatocyte membrane, in contrast to Gilbert's syndrome, is actively involved in the uptake of bilirubin. Treatment is similar to that of Gilbert's syndrome, phenobarbital is effective.

Differential diagnostic criteria for various functional hyperbilirubinemias are presented in table. 3.

Таблица 3. Дифференциальная диагностика функциональных гипербилирубинемий (по А.И. Кузнецову и соавт., 2001)

Синдром	Тип наследования	Патогенез	Клинические проявления	Лечение
Криглера — Найяра 1-го типа	Аутосомно-рецессивный	Отсутствие УДФГТ	Манифестация в первые часы жизни, ядерная желтуха тяжелого течения, билирубиновая энцефалопатия. Билирубин > 200 мкмоль/л	Фототерапия, трансплантация печени
Криглера — Найяра 2-го типа	Аутосомно-рецессивный	Снижение активности УДФГТ	Манифестация в первые месяцы жизни, ядерная желтуха средней степени тяжести. Билирубин < 200 мкмоль/л	Фенобарбитал, фототерапия
Жильбера	Аутосомно-доминантный	Снижение активности УДФГТ, нарушение захвата билирубина гепатоцитом	Чаще у мальчиков, манифестация в возрасте от 7 до 30 лет. Интермиттирующая иктеричность склер и кожи, редко диспепсия, астенизация	Фенобарбитал
Дабина — Джонсона	Аутосомно-доминантный	Нарушение транспорта билирубина в гепатоцит и из него	Чаще у мужчин в возрасте 25–30 лет. Желтуха, боли в правом подреберье, увеличение печени и селезенки	Нет
Ротора	Аутосомно-доминантный	Тот же, что при синдроме Дабина — Джонсона, и нарушение конъюгации билирубина	Чаще у мальчиков в пубертатном периоде. Желтуха, диспепсия, боли в правом подреберье	Нет
Люси — Дрисколл	Неизвестен	Наличие ингибитора УДФГТ в молоке матери	У детей первых дней жизни, находящихся на грудном вскармливании. Билирубиновая энцефалопатия	Отказ от грудного вскармливания
Доброкачественный семейный возвратный холестаз	Аутосомно-рецессивный	Гиперплазия лимфатических сосудов печени с развитием холестаза	Манифестация в неонатальном периоде. Интермиттирующее течение желтухи. Могут быть дегенеративные процессы ЦНС	Нет
Болезнь Байлера	Не известен	Перипортальный фиброз с нарушением оттока желчи	Манифестация в первые недели жизни. Выраженная желтуха, билирубин до 300 мкмоль/л	Нет

Since jaundice is a syndrome that accompanies various diseases, it should be treated symptomatically, with a focus on treating the underlying disease.

Basic principles of treatment

1. If the cause of jaundice is known, etiotropic treatment is carried out: treatment of viral hepatitis, removal of calculi, tumor resection, abolition of hepatotoxic drugs, deworming, surgical, endoscopic restoration of bile drainage (balloon dilatation of strictures, endoprosthetics, biliodigestive anastomoses).

2. Diet: limiting the use of neutral fats (up to 40 g per day with steatorrhea), triglycerides with an average chain length (up to 40 g per day).

3. Enzyme preparations, the gold standard of which is Creon.

4. Fat-soluble vitamins inside: K - 10 mg / day, A - 25 thousand IU / day, D - 400-4000 U / day. Intramuscularly: K - 10 mg per month, A - 100 thousand ME 3 times a month, D - 100 thousand ME per month.

With hypovitaminosis D, substitution therapy is prescribed at a dose of 50 thousand IU orally 3 times a week or 100 thousand IU intramuscularly 1 time per month (it is possible to use higher doses). If serum vitamin D levels are not controlled, the parenteral route is preferred over the oral route. In case of severe pain in the bones, a slow intravenous injection of calcium is prescribed (calcium gluconate, 15 mg / kg for several days), if necessary, with repeated courses.

Vitamins are indicated for the prevention of hypovitaminosis and hepatic osteodystrophy in jaundice and long-term cholestasis. It is necessary to take calcium preparations at 1.5 g per day, stay in the scattered rays of sunlight for the synthesis of vitamin D.

5. The drug of choice for non-obstructive cholestasis in many cases is ursodeoxycholic acid (UDCA). It makes up 0.1–5.0% of the total pool of bile acids and is non-toxic. When treating with ursofalk, ursosan, the proportions of the

constituent parts of bile shift towards a sharp predominance of UDCA over other bile acids. UDCA has a membrane stabilizing and hepatoprotective effect, protecting hepatocytes from the influence of damaging factors; has immunomodulatory activity; reduces the severity of immunopathological reactions in the liver by reducing the expression of histocompatibility antigens HLA-1 on hepatocytes and HLA-2 on bile duct cells and reducing the effect of immunoglobulins (primarily IgM); reduces the formation of cytotoxic T lymphocytes. Stimulating exocytosis in hepatocytes during cholestasis by activating Ca2 + -dependent α-protein kinase, UDCA reduces the concentration of bile acids toxic to hepatocytes (cholic, lithocholic, deoxycholic, etc.). UDCA inhibits the absorption of lipophilic bile acids in the intestine (apparently due to a competitive mechanism), increases their fractional turnover during hepatic-intestinal circulation; induces choleresis with a high content of bicarbonates, which leads to an increase in the passage of bile and stimulates the excretion of toxic bile acids through the intestine. Replacing non-polar bile acids, UDCA forms non-toxic mixed micelles. By reducing the synthesis of cholesterol in the liver, as well as its absorption in the intestine, UDCA reduces the lithogenicity of bile, lowers the cholato-cholesterol index,

UDCA is absorbed in the small intestine by passive diffusion, and in the ileum by active transport. The maximum concentration in blood plasma after oral administration is achieved in 0.5-1 hours. 96-99% binds to blood plasma proteins. The therapeutic effect of the drug depends on the concentration of UDCA in the bile. About 50–70% of the total dose of the drug is excreted in the bile, in the intestine it is partially broken down to lithocholic acid, which, during enterohepatic circulation, enters the liver and is re-transformed into heno- and UDCA. The optimal dose of UDCA is 10-15 mg / kg per day. The drug is taken for a long time.

6. For the treatment of itching of the skin, phenobarbital and (carefully!) Rifampicin are used until the effect is achieved and taking into account the toxic, sedative effect. For pruritus, cholestyramine, cholesterol, which bind pruritogens in

the intestinal lumen, are effective; drugs are prescribed in a short course in minimal doses, taking into account the possible deterioration in the absorption of fat-soluble vitamins. There is evidence of the effectiveness of opiate antagonists (nalmefene, naloxone), serotonin receptor antagonists (ondansetron), histamine H 1 receptor antagonists (terfenadine), as well as S-adenosyl-L-methionine (Heptral), which is involved in the detoxification of toxic metabolites and increases the level of cysteine, taurine, glutathione. For refractory itching, plasmapheresis, phototherapy (ultraviolet irradiation) are used.

In the treatment of Crigler-Nayyar syndrome type 1, phototherapy, phlebotomy, exchange transfusions of blood, albumin, plasmapheresis, liver transplantation, genetic engineering are used). Phenobarbital is ineffective. Phototherapy promotes the destruction of bilirubin in tissues. Frequent sessions of phototherapy (up to 16 hours a day) can prolong the life of patients; the method is effective in 50% of cases, it can be performed on an outpatient basis. However, even with a good effect of phototherapy, kernicterus can develop during the first two decades of life. Therefore, phototherapy should be considered as preparation for liver transplantation. Liver transplantation fundamentally improves the prognosis of the disease, as it helps to normalize the metabolism of bilirubin. Bloodletting, exchange transfusions, plasmapheresis, which are used to lower the level of bilirubin in the blood,

In type 2 Crigler-Nayyar syndrome, phenobarbital and phototherapy are quite effective.

Treatment for Dabin-Johnson and Rotor syndromes has not been developed.

The main treatment for Gilbert's syndrome and Meilengracht's syndrome is phenobarbital. Its effectiveness is explained by the fact that the drug induces the activity of UDPGT, promotes the proliferation of smooth endoplasmic reticulum, and an increase in the pool of Y- and Z-ligands. The disadvantages of phenobarbital are sedation, perversion of the metabolism of drugs excreted in the

form of glucuronides, stimulation of the metabolism of steroid hormones. Flumacinol, which is better known to practitioners under the trade name zixorin, also has the property of inducing the activity of UDPGT. However, the drug has long disappeared from Ukrainian pharmacies due to the expiration of the registration period. Thus, the real drugs shown in Gilbert's syndrome are galstena and citrarginine.