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# Biliary atresia in children (analytical literature review and review of own observation)

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## ABSTRACT

**Aim:** to review information resources and analysis of the own experience on this problem for the provision of modern knowledge in the pathogenesis of the pathology, the latest diagnostic and treatment technologies, with consideration of the need to adhere to a single strategy in the management of patients with BA.

**Materials and Methods:** The analysis of the data regarding the results of existing studies evaluating the clinical benefit and safety of diagnostic and treatment methods in Biliary atresia.

**Conclusions:** BA is the leading cause of neonatal cholestasis development. Early diagnostics of BA, based on the complex evaluation of clinical-laboratory, instrumental and morphological signs of the pathology, has a significant meaning. Surgical correction during the first 2 months of life – the Kasai procedure, as well as dynamic post-surgery follow-up significantly prolong the life of children and allow postponing liver transplantation. The highest patient survival both at the first stage of treatment – conduction of the Kasai procedure and the stage of liver transplantation may be achieved by joined work of surgeons and pediatricians, which allows considering the whole row of possible problems.

**KEY WORDS:** biliary atresia, infants, diagnostics, treatment

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## INTRODUCTION

Biliary atresia (BA) is one of the most frequent causes of the development of neonatal cholestasis. It is an intrahepatic and/or extrahepatic inflammatory cholangiopathy of still uncertain pathophysiology leads to biliary duct obliteration during the first weeks of life, progressive liver fibrosis, secondary biliary cirrhosis, and eventually death, if not treated in a timely fashion. [1, 2] Nowadays, BA remains one of the pathologies of infants, which is extremely difficult to treat. Despite the number of studies dedicated to the problem of BA, the number of publications related to clinical recommendations for this pathology treatment is limited. Progressive obliteration of extrahepatic bile ducts with gradual involvement of intrahepatic bile duct injury and formation of biliary liver cirrhosis lies at the basis of the disease [3]. Without surgical intervention, BA causes the death of the child during the first 2 years of life. In recent decades, significant progress in the treatment of children with BA was achieved – timely Kasai's operation, and in case of its inefficiency – liver transplantation increased the survival of patients with BA to 90% [4-6].

## AIM

The aim of the article is the review of information resources and analysis of the own experience on this problem for the provision of modern knowledge in the pathogenesis of the pathology, the latest diagnostic and treatment technologies, with consideration of the need to adhere to a single strategy in the management of patients with BA.

## MATERIALS AND METHODS

The analysis of the data regarding the results of existing studies evaluating the clinical benefit and safety of diagnostic and treatment methods in Biliary atresia.

## REVIEW AND DISCUSSION

### EPIDEMIOLOGY

According to the data of epidemiological studies, the frequency of cholestatic jaundice is approximately 1:2500 infants and the incidence of BA in different

countries of the world varies from 1:3500 to 1:20000 live-born children [7]. BA is more frequent in Taiwan and Japan, compared to North America and Europe. Several studies have found that the highest incidence of BA is in African-American children. The evidence concerning gender differences in BA incidence is not convincing. BA amounts to approximately 8% of all defects of internal organs in children. According to some data, BA incidence is higher in premature infants [6-8]. Children with BA and developmental defects in other body systems are not frequent; there is also data about single episodes of association of BA with chromosomal abnormalities [9]. In most episodes, BA is isolated or related to other hepatobiliary pathologies and developmental defects [10].

### HISTORICAL ASPECTS

The first notice about BA was published by J. Burns in 1817 [11]. The author wrote that the presence of jaundice during the first months of life may indicate a serious danger to the life of the child, especially if the white colour stool is observed, and the most possible reason for this is biliary system obstruction. Later, in 1852, C. West presented a detailed description of clinical symptoms of this disease in a 13-week-old girl, who was born to healthy parents, and on the 3rd day of life, she developed jaundice, which was gradually increasing, as well as white-color cream-like stool and dark urine. In 1891, J. Thomson defended a thesis, dedicated to the issues of the clinical presentation and pathological anatomy of congenital obliteration of the bile ducts. The work was based on his experience of observation of 50 children with this pathology. The author concluded about the primary lesion of extrahepatic bile ducts with gradual involvement of the intrahepatic bile system with the formation of biliary liver cirrhosis [12]. In 1916, J. B. Holmes dedicated the work to diagnostics and treatment of congenital obliteration of bile ducts, in which the author paid attention to the danger of the pathology which leads to biliary cirrhosis with lethal outcomes [13].

In 1928, W. E. Ladd et al. made the first attempt at surgical correction of BA in Boston. 11 children underwent surgeries, and it was concluded that in the case of conduction of surgical intervention conduction at the age before 4 months of life clinical and laboratory manifestations of the disease decreased [14]. By 1946, 146 with BA underwent surgery in Boston Children's Hospital. During surgery, the doctors managed to staple anastomosis between bile ducts and duodenum only in 27 patients. Herewith, jaundice disappeared only in 12 patients, and the condition of 15 children

deteriorated after surgery and led to lethal outcomes [15]. Hepatoportoenterostomy operation, which was developed by M. Kasai and S. Suzuki in the 50s of the last century, remains the main method for the treatment of children with BA [16]. The surgical intervention, which nowadays is named after Kasai, is based on the idea that the intrahepatic bile ducts persist in early childhood and are located in the cone-shaped fibrous tissue of the porta hepatis. In the 1970s, professor M. Kasai (Japan) studied pathological changes in intrahepatic and extrahepatic bile ducts in children with BA, as the result of which two important conclusions were made: 1) the process of destruction of intrahepatic bile ducts with the development of a pseudo-ductular proliferation of the portal tracts is progressively increasing during the period of 2nd to 12th week of the life; 2) histological signs, indicating on the preservation of the integrity of intrahepatic bile ducts in the area of the porta hepatis, is a favorable indicator of the prognosis. In this situation, renewal of the patency of the extrahepatic bile ducts prevents further obliteration of the intrahepatic bile ducts [17, 18].

In 1974 M. Kasai offered the classification, which described two types of BA: type I – BA, which can be corrected (bile ducts or cystic formations with thick bile in porta hepatis) and type II – BA, which cannot be corrected (is characterized by the absence of bile ducts in porta hepatis [17].

### AETIOLOGY AND PATHOGENESIS

The extrahepatic bile system is known to originate from the caudal part of the liver bud approximately at 4 weeks of gestation. Hepatocytes and cells of intrahepatic ducts stem from the cranial part. The bile begins to secrete into the duodenal tube before 12–14 weeks. Development of BA may be the result of abnormal morphogenesis of bile ducts or lesions of normally formed ducts. The process of obliteration of extrahepatic bile ducts was found to take place during the first trimester of pregnancy. Later, on the further terms of intrauterine development, circulation of the bile of the foetus occurs with the participation of the placenta and intestines of the mother. Only a small amount of it comes into non-formed bile ducts, causing the inflammatory reaction of surrounding tissues. Therefore, the most vivid presentation of the disease develops after birth, when the mother's organism is excluded from the process of bile circulation [19, 20]. Nowadays, the etiology and pathogenesis of BA remain not studied completely [10, 21]. Different theories are discussed: theory of developmental abnormality, viral, genetic, etc. According to the theory of developmental abnormality, the absence

of canalization of the primary epithelial lining in the embryonic stage may take place. The possibility of a combination of several defects of development indicates this theory. However, defects of the bile system may be the result of infection, intoxication, and other pathological factors, influencing morphogenesis in the early terms of intrauterine development [22]. Most children with BA have meconium, coloured with bile, which allows assuming normal primary development of bile ducts and practically excludes the theory of development abnormality [23, 24].

Data from experimental studies indicate an interconnection between the persistence of cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, human papillomavirus, and reovirus type 3 and the development of BA. A relation between virus hepatitis A, B, C and the development of BA was not found [25-27]. The infectious etiology of the pathological process was first assumed in 1965 by

H. Stern and S.M. Tucker, who distinguished CMV in a patient with BA [28]. The infectious etiology of BA was studied by B.H. Landing, who developed the conception of perinatal obliterating inflammation of the bile system with the involvement of both extrahepatic and intrahepatic ducts. The author assumed that neonatal hepatitis, BA, and cyst of the common bile duct are manifestations of one inflammatory process developing at different stages of intrauterine development [29].

Nowadays, studies on the role of the immune system in the pathogenesis of BA are conducted. Some observations indicate the possibility of genetic predisposition to the development of BA [30, 31]. The main etiological cause of the embryonic type of BA is considered to be gene mutation, which causes pathological morphogenesis of the biliary tree. According to many researchers, perinatal BA is acquired, and not the congenital pathology. In the case of perinatal BA, the biliary system develops regularly, but later it undergoes the influence of provocative factors, leading to obliteration of the biliary tract (viruses, toxic ecological factors, blood supply disorders). The most frequent factor of BA formation is CMV, the DNA of which is found in liver biopsy slides in 80% of episodes. Based on the literature data, it is possible to conclude that according to its etiology, BA is a heterogeneous disease and shall be considered a general condition of various disorders [10].

## CLINICAL MANIFESTATIONS OF BA

In most cases, children with BA are born at full-term and have anthropometric indicators corresponding to the normal range. Obtaining a detailed family history (neonatal cholestasis in parents or siblings, fetal loss

or early death of a child in the anamnesis, hemolytic diseases, etc.), prenatal and postnatal history (prenatal results of USD, cholestasis of pregnancy, acute fatty liver of pregnancy, maternal infections), data about neonatal screening (general health condition disorders, neonatal infection, stool and urine color, hemorrhage, etc.), having increased risk of probable BA is compulsory. Based on our observations, family history was burdened in 20% of children with BA.

Jaundice develops on the 2<sup>nd</sup> – 3<sup>rd</sup> day of life, which is in regular terms for physiological jaundice. Approximately 23 studied patients had a "light period" – reduction of jaundice intensity by the end of 1–2 weeks of life with its gradual increase and development of the greenish shade by the end of the 1st month. Acholic stools are the earliest and constant clinical symptom of the disease. The urine is dark.

The characteristic feature of BA is the absence of hepatomegaly at birth with further enlargement of the dimensions of the liver and changes in its consistency from elastic to dense during the first 2 months of life [4, 33].

Development of haemorrhagic syndrome (hemorrhage from mucous membranes of the gastrointestinal tract, umbilical wound, intracranial hemorrhages), caused by the deficiency of vitamin K-dependent coagulation factors as the result of the violation of the process of vitamin K absorption in the intestine is possible approximately at the 1st month of life, what we observed in 60% of patients. Absorption of fat-soluble vitamins is known to take place with the participation of bile, which does not come into the intestinal tract in the case of BA. The weight deficit, as a rule, is formed at the age of 1–2 months, and the degree of its expression depends on the nutrition of the child. The most expressed deficit is observed in the case of breastfeeding or the use of milk formula, recommended for feeding healthy infants. In the case of nutritional care, weight deficit can be absent or minimally expressed [32].

Without surgical treatment, signs of portal hypertension appear yet before 5–6 months together with skin itching and xanthomas, which progressively grow and indicate the formation of biliary liver cirrhosis [33].

The earliest laboratory indicator of BA is bilirubin increase due to the direct fraction in the blood serum, which amounts to 20% of the level of bilirubin total. An increase in other biochemical markers of cholestasis (gamma-glutamyl transferase GGT,  $\beta$ -lipoproteins, cholesterol, alkaline phosphatase, bile acids, etc.) is typical, and the level of its expression increases in dynamics from the minimal increase in first 2–3 weeks of life to significant increase before 2-3 month of life. GGT ferment is especially indicative, as its level may be exceeded more than 20 times. Cytolysis ferments (ALT,

AST) are moderately increasing, which is delayed as a rule. In most episodes of BA, these parameters remain within the normal range during the first 2–3 weeks after birth. Parameters, reflecting the protein-synthetic function of the liver (albumin, fibrinogen, PTI, etc.) change at the early stages of the disease. The finding of low levels of PTI in these patients reflects disturbances of the processes of vitamin K absorption in the intestinal tract, which are renewed well in the case of vikasol use [34].

Special attention should be given to the fact that patients with BA do not have specific anamnestic or clinical symptoms. A thorough examination has a decisive meaning for the appropriate evaluation of jaundice in a neonate and infant. Diagnostic examination in any child with prolonged jaundice (after 14 days in full-term infants and after 21 days in premature infants with a clear tendency to reduction) shall include evaluation of the family history, pregnancy anamnesis, clinical examination and monitoring of the stool color. While evaluating the color of the stool, it is important to remember that the use of certain formulas may influence the color of the stool. In such a way, according to our observations, Humana low-lactose with medium chain triglycerides, Alfare, Pregestimil, Nutrillon, etc. give the stool different shades of gray – from light to dark gray.

## LABORATORY DIAGNOSTICS OF BA

During BA diagnostics, obtaining of detailed family history of neonatal cholestasis in parents or siblings, fetal loss or early death of a child in the anamnesis, haemolytic diseases, etc.), prenatal and postnatal history (prenatal results of USD, cholestasis of pregnancy, acute fatty liver of pregnancy, maternal infections), data about neonatal screening (general health condition disorder, neonatal infection, stool and urine color, hemorrhage, etc.), having increased risk of probable PA is compulsory.

An increased level of direct (conjugated) bilirubin for more than 20  $\mu\text{mol/l}$  or for more than 20% of the level of the bilirubin total is observed in the blood of children with BA. Conjugated bilirubin is found in urine. Urine does not contain urobilin, as it is not formed and cannot come into the intestinal tract [35].

Cytolysis ferments (ALT, AST) are moderately increasing with a delay. In most episodes of BA, these parameters remain within the normal range during the first 2–3 weeks after birth, and then they gradually increase with the progression of hepatocyte cytolysis. The increased level of biochemical markers of cholestasis – plasma beta-lipoproteins, cholesterol, alkaline phosphatase, and bile acids. In coagulogram - signs of hepatic coagulopathy: reduction of prothrombin, fibrinogen, prothrombin time, and activated partial thromboplastin time [36].

Determination of the level of GGT (gamma-glutamyl transferase) in blood serum, which is significantly increased in case of this disease (almost 20 times) has significant meaning in establishing the diagnosis of BA [2, 4, 37]. EIA test for the detection of intrauterine infection detects CMV infection in 80% of the cases [38].

## INSTRUMENTAL DIAGNOSTICS

### ULTRASOUND

A characteristic triad of ultrasound signs of BA: hypoplasia or absence of the gallbladder; triangular cord sign at the fibrous area in the porta hepatis above the portal vein bifurcation associated with periportal fibrosis of the liver parenchyma, increase in the diameter of the hepatic artery.

Ultrasound of the abdominal cavity is appointed to exclude a choledochal cyst and gallstone disease, which cause obstruction of extrahepatic biliary ducts. Contraction of the gallbladder after feeding excludes BA. In some cases of BA, extended intrahepatic bile ducts are detected, cysts in porta hepatis are less frequent. It is important to note that the informativeness of ultrasound significantly decreases in children after 3 months of life [33]. Among children with BA, studied by us, 2 patients developed polysplenia.

### HEPATOBIILIARY SCINTIGRAPHY

In BA, absorption and accumulation of nucleotides by hepatocytes are rapid, however, there is no excretion into the intestinal tract, even on the postponed scans. Analysis of the excretion of isotopes is not sufficiently informative to differentiate BA from other cholestatic liver diseases, which may lead to the delay in diagnosis establishing due to the necessity of pre-test administration of phenobarbital. However, demonstration of the present bile excretion may be valuable while establishing a diagnosis [34].

**MRI.** The criteria of BA are considered to be the bile duct, which is not visualized, and the small dimensions of the gallbladder. Certainly, MRI is a prospective method of hepatobiliary system visualization. MRI is the most accurate non-invasive examination method, allowing diagnosis to be established almost without error [33, 35].

**Intraoperative liver biopsy** – wedge-shaped excision of the particle of parenchyma with the purpose of histological examination – applied in all children with BA [36].

**Prenatal diagnostics.** Low GGT level in amniotic fluid at the 18<sup>th</sup> week of gestation may be a sign of BA [35, 37].

**Table 1.** Causes of neonatal cholestasis

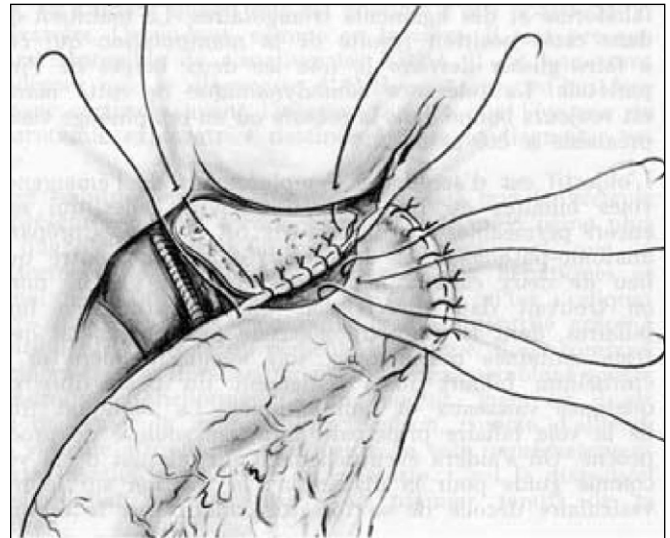
<p><b>Extrahepatic cholestasis</b></p> <p>Atresia of extrahepatic bile ducts (biliary atresia)</p> <p>Common bile duct cyst</p> <p>Gallstones and bile duct stones</p> <p>Compression of the common bile duct</p>
<p><b>Intrahepatic cholestasis</b></p> <p><u>Progressive familial intrahepatic cholestasis (PFIC)</u></p> <p>Type 1 (Byler disease)</p> <p>Type 2 (Byler syndrome)</p> <p>Type 3 (MDR3 deficiency)</p> <p><u>Benign familial intrahepatic cholestasis</u></p> <p><u>Metabolic disorders</u></p> <p>Alpha-1 antitrypsin (AAT) deficiency</p> <p>Galactosemia</p> <p>Fructosemia</p> <p>Tyrosinemia</p> <p>Bile acid synthesis disorders (BASD) due to enzyme defects</p> <p>Peroxisome deficiency (Zellweger syndrome),</p> <p>Neonatal haemochromatosis</p> <p>Niemann-Pick disease type C</p> <p>Mitochondrial insufficiency</p> <p><u>Infectious diseases (virus, bacterial, caused by protozoa)</u></p> <p><u>Endocrine disorders</u></p> <p>Hypopituitarism</p> <p>Hypothyroidism</p> <p><u>Chromosomal disorders</u></p> <p>Trisomy 13, 17 or 18 chromosomes</p> <p>Cholestasis induced by total parenteral nutrition</p> <p><u>Drug-Induced Cholestasis</u></p> <p><u>Other</u></p> <p>Alagille syndrome</p> <p>Non-syndromic intrahepatic bile duct hypoplasia.</p> <p>Perinatal sclerosing cholangitis</p> <p>Idiopathic neonatal hepatitis</p>

**Liver macroscopy in biliary atresia.** The color of the external surface of the liver changes from green to dark green in 81% of clinical observations. In 19% of cases, the color of the liver varies from yellow-green to red-brown. The surface of the liver and parenchyma are fine-grained. In 43% of cases, the extension of intrahepatic bile ducts occurs, and cyst cavities closer to the porta hepatis contain thick biliary sludge. The choledoch duct has either a form of fibrous cord (76.2% cases) or is hypoplastic (23.8% of observed cases). The gallbladder has either a form of fibrous cord (66.7% of cases) or hypoplastic (33.3% of cases).

## HISTOLOGICAL STUDIES OF THE LIVER IN BILIARY ATRESIA

The most characteristic histological changes of the liver in BA are:

- cholestasis in hepatocytes and bile ducts
- proliferation of bile ducts
- giant transformation of hepatocytes
- portal oedema



**Fig. 1.** Kasai Procedure (hepatoportoenterostomy).

- liver fibrosis and cirrhosis
- absence of diagnostic signs of other diseases of the liver of an infant.

The degree of morphological changes depends on the age of the child and increases with age [38].

Diagnostic accuracy of the examination methods of BA:

- Liver biopsy - 96.9%
- Clinical-laboratory study - 70.8%
- Ultrasound 69,2%
- Scintigraphy – 58.5% [33, 34, 38].

Examination by medical specialists Purposeful establishment of the diagnosis in neonates and infants with jaundice should also be based on the examination by the medical specialists aimed at differential diagnosis conduction of the pathology: geneticist, ophthalmologist, cardiologist, infectious disease specialist, etc. Radiography of the lungs and heart, diagnosis of vertebral and spinal anomalies, echocardiography, etc. are recommended.

Differential diagnosis of BA is conducted with other liver and bile duct diseases, which manifest as cholestasis syndrome (Table 1).

## SURGICAL CORRECTION

Surgical modifications of the Kasai (hepatoportoenterostomy) include removing the structures, located in the area of porta hepatis, and conducting the resection of the fibrous residue of the bile duct at this level. This resection opens the lumen of the preserved bile ducts, which remain passable [14, 15, 32]. For applying biliary-intestinal Y-anastomosis the loop of the small intestine (Fig. 1).

The efficiency of this procedure depends on several factors: age of the child, expression of cirrhosis changes, number of functioning bile ducts in porta hepatis,

presence of developmental defects of other organs, surgeon's experience, post-surgery follow-up of the patient, etc.

One of the main factors influencing the efficiency of the Kasai procedure is the age of the child at the moment of surgical intervention. The most optimal age for the procedure is the first two months of life. According to R. Ohi et al., jaundice clearance after the surgery is observed in 80% of children at the age under 2 months [32]. In the case of procedure conduction at an older age, its efficiency reduces.

We have experience of surgical correction of BA using Kasai procedure in 36 patients. To prevent cholangitis we use a modified Kasai procedure - invaginated hepatic porto-jejunosomy (creation of an invaginated valve in the biliary area of the intestinal tract).

## COMPLICATIONS AFTER KASAI PROCEDURE

There exists a probability of the development of cholangitis, portal hypertension, hepatopulmonary syndrome or pulmonary hypertension, intrahepatic cysts and tumors after the Kasai procedure. The early detection and timely correction of these complications have a very significant meaning [1-3].

Direct connection of intrahepatic bile ducts with the intestinal tract leads to the infection and development of *cholangitis*, which may be observed both during the first weeks and months and in the distant future. Prophylaxis of cholangitis includes long-term use of bactrim for 3–6 months with a gradual transition to lower use under the condition of the absence of inflammatory changes in total and biochemical blood tests, 2–3 days per week for 3–6 months. Cholangitis treatment includes parenteral administration of antibacterial and/or antiviral medication and conduction of non-specific syndromic therapy. Development of cholangitis in a delayed post-surgery period may be associated with the formation of intestinal reflux, stoma obstruction, as well as the result of cyst infection. Detection of the surgical cause of this complication is the indication for repeated surgery, while in other situations antibacterial therapy is appointed.

Portal hypertension develops in approximately 2/3 of children after portoenterostomy.

In case of adequate bile passage, varicose veins treatment is conducted in the form of sclerotherapy or vein ligation.

Release of vasoactive substances from the intestine after surgery or a decrease in their clearance in porto-systemic shunts can lead to the development of pulmonary arteriovenous shunts or pulmonary hypertension.

Intrahepatic cysts may develop within several months or years after the Kasai procedure. Cysts of the liver may not have any clinical manifestations, however, there is the risk of their infection and portal vein compression. In such a situation, antibacterial therapy or surgical correction is recommended.

Hepatocarcinoma, hepatoblastoma and cholangiocarcinoma were described in children after the Kasai procedure. Due to this, the patients should undergo examination, allowing detection of a tumor at the early stages of its development.

Obstruction of bile outflow. In such situations, repeated surgical intervention with the revision of porta hepatis may be conducted.

## INDICATIONS FOR LIVER TRANSPLANTATION

1. Portal hypertension, especially in the events of hemorrhages
  2. Recurrent cholangitis
  3. Recurrent jaundice and/or liver failure syndrome
  4. Suspicion of hepatocellular carcinoma
  5. Significant physical and mental development delay
- Liver transplantation is the main method of treatment for children with BA due to life-threatening complications. Liver transplantation is considered to be more appropriate than Kasai portoenterostomy in the case of BA in many transplantation centers in the world [39, 40].

## CONCLUSIONS

Thus, BA is the leading cause of neonatal cholestasis development. Early diagnostics of BA, based on the complex evaluation of clinical-laboratory, instrumental and morphological signs of the pathology, has a significant meaning. Surgical correction during the first 2 months of life – the Kasai procedure, as well as dynamic post-surgery follow-up significantly prolong the life of children and allow postponing liver transplantation. The highest patient survival both at the first stage of treatment - conduction of the Kasai procedure and the stage of liver transplantation may be achieved by joined work of surgeons and pediatricians, which allows considering the whole row of possible problems.

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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