ОГЛЯДИ

UDC 616.36-004-008.6-002.1:616.37-006.5]-06-092

Pathophysiological features of acute liver failure caused by cholestasis

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Acute liver failure is a syndrome that occurs in 20-59% of patients with liver pathology and is one of the main causes of death in 40% of patients with mechanical jaundice of benign origin and in more than 70% of cases of tumor obstruction of the biliary tract and cancer of caput pancreas. In most cases, the syndrome is a consequence of acute liver damage (viral or drug-induced). Still, it can occur with long-term obstructive jaundice, be the first manifestation of Wilson's disease, autoimmune chronic hepatitis, or superinfection of the hepatitis D virus against the background of chronic hepatitis B. The aim of the work was to study the pathophysiological features of the development of acute liver failure in patients with bile outflow disorders. The pathogenesis of acute liver failure caused by cholestasis is based on the damage and death of hepatocytes due to impaired blood circulation in the liver, as well as the toxic effect on the parenchyma of both the etiological factors themselves and their metabolites. The first week from the onset of symptoms is very important and usually accompanied by a systemic inflammatory response syndrome with significant consequences. At the same time, the main factors influencing the results of treatment of patients at different points in time are the combination of the critical functional reserve of the liver and the nature and severity of liver damage. In the case of the development of a systemic inflammatory response syndrome, there is a further increase in inflammation, which has a systemic nature and leads to the failure of other organs. Under these circumstances, understanding the pathophysiological features of the course of acute liver failure makes it possible to carry out the necessary diagnostic measures on time and offer appropriate therapy.

Key words: acute liver failure; cholestasis; cirrhosis; hepatitis; pancreatic cancer.

INTRODUCTION

According to the recommendations of the European Association for the Study of the Liver (EASL, 2017) and the American Association for the Study of Liver Diseases (AASLD, 2017, 2023), acute liver failure (ALF) is defined as a syndrome of rapidly progressive liver dysfunction, which associated with a high risk of mortality. The frequency of development of this syndrome in patients with liver pathology is 20-59%, while it is one of the main causes of death in 40% of patients with mechanical jaundice of benign origin and in more than 70% of cases of tumor obstruction of the biliary tract [1]. The main features of ALF are hepatic encephalopathy (HE), coagulopathy (international normalized ratio (INR) >1.5), and jaundice, which develop in patients without a history of liver disease. At the same time, the Asian Pacific Association for Study of Liver (APASL, 2021) defined this condition as a syndrome with acute liver damage manifested by jaundice (serum bilirubin ≥85 μmol/l) and coagulopathy (INR ≥1.5 or prothrombin activity <40%) and complicated within 4 weeks by ascites and/or HE in a patient with previously diagnosed or undiagnosed chronic liver disease with high 28-day mortality [2].

Together with the term «acute liver failure» to define a similar clinical condition, the term «fulminant (lightning) liver failure» (FLF) is

found in the literature. For the first time in 1970, it was used by C.Tray and L.Davidson in relation to a clinical syndrome characterized by severe liver dysfunction due to massive necrosis of hepatocytes and in the absence of previous damage to the organ [3]. Later, this characteristic was modified, and now it is believed that ALF can develop on the background of some asymptomatic liver diseases [4]. The main feature of FLF is the presence of jaundice and HE, which develops within 8 weeks after the onset of jaundice. Under these circumstances, the development of pronounced coagulopathy (a decrease in INR and activity of blood coagulation factor V >50% of the norm), an increase in the activity of alanine aminotransferase and aspartate aminotransferase by 2-3 times, and a different degree of severity of HE in people with no history of liver diseases are noted. At the same time, an important criterion for the diagnosis and classification of ALF is the time from the first manifestations of liver disease (or jaundice) to the development of HE (Fig. 1) [5].

In most cases, ALF occurs as a result of acute liver injury (viral or drug-induced), but it can be the first manifestation of Wilson's disease, autoimmune chronic hepatitis, or hepatitis D virus (HDV) superinfection on the background of chronic hepatitis B [6]. In addition, long-term obstructive jaundice also provokes the development of ALF [7]. It is established that in such cases, liver dysfunction occurs with hepatorenal, hemorrhagic syndromes and HE, which leads to acute hepatic and then multiple organ failure (MOF) and death. The treatment program for patients in such cases involves mandatory decompression of the biliary system [8].

Therefore, the study of the main pathogenetic links in the development of ALF in patients with disorders of biliary patency will allow us to determine the main predictors of the development of this complication and to start the treatment of this extremely difficult category of patients in a timely manner.

The purpose of this work was to study the pathophysiological features of the development of acute liver failure in patients with bile outflow disorders.

Etiology of acute liver failure. The most common causes of ALF in adults are drug-in-

Organ failure	Asian Pacific Association for the Study of the Liver	European Association for the Study of Liver-Chronic Liver failure organ failures definition Based on CLIF-C ACLF score	North American Consortium for Study of End-stage Liver Disease organ failures definition
Liver	Total bilirubin ≥5 mg/dL INR ≥1.5	Bilirubin >12 mg/dL	–
Coagulation	INR ≥1.5	INR ≥2.5	–
Kidney	AKIN criteria Creatinine: increase > 0.3 or 1.5-fold over 48 h to: >/= 0.7 & 1.5	Creatinine level of ≥2.0 mg/dL or renal replacement	Need for dialysis or other forms of renal replacement therapy
Brain	HE (West-Haven) grade 3–4	HE (West-Haven) grade 3–4	HE (West-Haven) grade 3–4
Circulation	–	Vasopressor usage (terlipressin and/or catecholamines)	Shock with MAP <60 mm of hg or drop of >40 mm of Hg from the baseline despite adequate fluid resuscitation
Respiration		PaO_2/FiO_2 of ≤200 or SpO_2/FiO_2 of ≤214 or mechanical ventilation	Need for mechanical ventilation

Organ dysfunction defined as (coagulation–INR >1.5, Renal–creatinine [1.1–1.5 mg/dL], cerebral [HE grade I–II], circulatory–<Systolic BP <70 mm of Hg, respiratory PaO_2/FiO_2 200–300).
CLIF C-ACLF, chronic liver failure consortium acute-on-chronic liver failure; INR, international normalised ratio; AKIN, acute kidney injury network; BP, blood pressure; HE, hepatic encephalopathy; MAP, mean arterial pressure.

Fig. 1. Definition of acute liver failure (V.K.Br et al., 2023)

duced and viral liver damage. Thus, in Australia, Denmark, Great Britain and the USA, one of the main etiological factors of ALF is the toxic effect of acetaminophen (proven hepatotoxicity at a dose of >10 g per day), while in Asian countries and some European countries, it is hepatotropic viruses [9]. Cases of toxic concentrations of acetaminophen entering the body are described more often when taking the drug with suicidal intent, or when it is simultaneously prescribed with other drugs, especially when used for pain relief.

In the development of ALF, the main role is given to hepatitis A, E, B, D and C viruses, to a lesser extent to adenoviruses, herpesviruses (cytomegalovirus, Epstein-Barr virus, herpes viruses of types 1, 2, 3). Hepatitis A (HAV) and E (HEV) viruses have a fecal-oral transmission mechanism. Most often, severe liver damage is observed in endemic regions. In the USA, ALF caused by HAV accounts for up to 4% of cases [10]. HEV causes the development of ALF mainly in pregnant women in endemic countries, increasing the mortality from this pathology from 15% to 25% [11]. In many other regions that are not considered endemic, the role of this virus in liver damage requires further investigation. Thus, in European countries, when analyzing the etiology of cryptogenic ALF in hospitalized patients, HEV was detected in 10% of cases [12]. In some Asian, Mediterranean, and European countries, hepatitis B virus (HBV) is the most common cause of ALF, and in the United States, HBV accounts for up to 8% of all ALF cases [13]. The question of the role of the hepatitis C virus (HCV) in the occurrence of this pathology is still a subject of debate [14].

Rare pathogens capable of causing ALF include cytomegalovirus (described in a liver transplant (LT) recipient receiving immunosuppressive therapy who was previously infected with the virus) and Epstein-Barr virus. In the literature, there are indications of ALF caused by herpes viruses of types 1, 2 and 3 mainly in persons with immunosuppression on the background of taking glucocorticoids, in patients with oncological diseases, HIV infection, myelodysplastic syndrome, after transplantation (more often with simultaneous damage to several organs), in pregnant women [15]. Under these circumstances, herpetic rashes on the skin occur only in 50% of the described cases. There are also data on the development of ALF against the background of infection with adenoviruses of group C type 5 and parvovirus B19 in patients with immunosuppression [16].

Drugs and toxins cause the development of ALF in 5-18% of cases, with 80% of episodes leading to death or requiring emergency LT [17]. Chemical substances that enter the body from the environment in large doses (dose-dependent toxicity), but in some patients - in therapeutic doses (idiosyncratic hepatotoxicity), can have a toxic effect on the liver. Clinical cases of ALF after taking some food supplements and medicinal plants are described. Under these circumstances, the hepatocellular lesion has the character of ALF, with a cholestatic character - subacute liver failure and a fulminant course is observed in less than 30% of cases (usually due to the use of narcotic drugs).

Risk groups also include patients taking antituberculosis drugs (for example, isoniazid), nitrofurans, ketoconazole, phenytoin, valproate, and nonsteroidal anti-inflammatory drugs [18]. At the same time, reactions accompanied by systemic manifestations (fever, rash, enlarged lymph nodes) and eosinophilia are rare and are usually due to the use of sulfonamides, anticonvulsants, and antibiotics [19]. In isolated cases, the cause of liver damage is hypoperfusion caused by taking long-acting niacin, cocaine, or methamphetamine [20].

Mushroom poisoning in 95% of cases is caused by Amanita phalloides and Galerina annually kills hundreds of people in Europe and the USA. Amanita contains two toxins: phalloidin and α-amanitin (both are hepatotoxic). Poisoning is caused mainly by α-amanitin, which has a dose-dependent, direct hepatotoxic effect on the liver, disrupting mRNA synthesis in hepatocytes [21].

Autoimmune hepatitis manifests as ALF

rarely but is characterized by a severe and rapidly progressive course. The presence of hypergammaglobulinemia, autoantibodies in the blood serum helps to establish the correct diagnosis, but sometimes the latter may be absent, which complicates the diagnosis of the disease [22]. To confirm the diagnosis in certain cases, it is necessary to use a puncture biopsy of the liver.

Wilson's disease is a rare cause of ALF (2-3% of cases), observed most often in young women. Under these circumstances, ALF has a rapid course with a high mortality rate and is characterized by sudden hemolytic anemia (with a negative Coombs reaction), an increase in the level of bilirubin (mainly due to the indirect fraction), with low or normal values of alkaline phosphatase and a moderate increase in aminotransferases. The ratio of aminotransferases is often >2, and coagulopathy is not corrected by the introduction of vitamin K. When establishing a diagnosis, it is necessary to take into account: the level of ceruloplasmin (usually reduced, but in 15% of patients it remains normal); copper content in blood serum and urine (usually high); the ratio of total bilirubin and alkaline phosphatase (>2 - an indirect indicator of Wilson's disease); presence of Kaiser–Fleischer rings; copper content in liver biopsy [23].

Thrombosis of the hepatic veins (Budd-Chiari syndrome) is a polyetiological disease, that often occurs in patients with malignant diseases of the blood system during chemotherapy in preparation for bone marrow transplantation, in myeloproliferative syndrome, deficiency of blood coagulation factor V, protein S or antithrombin III. Rare causes of the disease include radiation damage and the toxic effect of some drugs containing herbs. In 20% of cases, Budd-Chiari syndrome occurs in women who take contraceptives (for at least 2 weeks), in pregnant women, and women in the postpartum period [24]. Patients develop hepatomegaly, abdominal pain, and ascites, the diagnosis is established using computed tomography (CT), Doppler, and magnetic resonance angiography [25].

The development of ALF against the background of ischemic liver damage can be caused by cardiogenic shock during acute myocardial infarction, a long period of cardiopulmonary resuscitation during cardiac arrest, a period of significant hypovolemia/hypotension, or decompensation of chronic heart failure [26]. At the same time, physical changes in patients may be absent or be detected only on the ECG. Usually, when examining a patient, a significant increase in the level of aminotransferases is observed, with a tendency to a rapid decrease when hemodynamics stabilizes. The prognosis for this contingent of patients is determined by the pace of heart failure correction and elimination of other causes of ischemia.

Tumor damage to the liver is observed in breast cancer, small cell lung cancer, lymphoma, and melanoma, and can lead to the development of ALF [27]. In this regard, patients with a history of malignant neoplasms should undergo a thorough examination using a CT scan of the internal organs, as well as a puncture biopsy of the liver, to clarify the diagnosis.

If there is an increase in the activity of aminotransferases in the blood plasma and/or the presence of cholestasis syndrome in the absence of obvious primary liver damage, the patient must be examined to identify possible secondary damage, which is observed in a number of diseases: sepsis, malaria, leptospirosis, rickettsiosis, hyperthyroidism, Still's disease, hemophagocytic syndrome [28]. In the latter two diseases, the level of ferritin increases significantly, and in hemophagocytic syndrome, the level of triglycerides also increases.

Cholestasis and its role in the development of liver failure. One of the factors in the development of ALF is a violation of the patency of the biliary tract (cholestasis), both of benign and malignant origin (7:3). Cholestasis is defined as a violation of the outflow of bile caused by diseases of hepatocytes, intrahepatic bile ducts or extrahepatic biliary system. Violation of bile secretion for any reason leads

to its accumulation (bilirubin, bile acids and lipids) in the liver, which, as a result, causes an increase in the level of bilirubin and bile salts in the blood, as well as changes in lipid metabolism. Clinically, patients usually have jaundice, clay-like stools, itching, and bleeding episodes. Chronic cholestatic liver disease can progress to cirrhosis and liver failure and is the leading cause of LT in children. According to anatomical localization, cholestasis is divided into extrahepatic and intrahepatic. Extrahepatic cholestasis is caused by structural abnormalities of the biliary tract, including obstruction of the bile ducts and gallbladder. Surgical treatment is usually used to restore physiological function. However, intrahepatic cholestasis is more complex and usually requires a careful examination of the patient. Common causes of extrahepatic and intrahepatic cholestasis are shown in Fig. 2 [29].

Cholestasis is a common manifestation of hepatic metabolic disorders, including carbohydrate, amino acid, and fat metabolism, as well as mitochondrial and endocrine abnormalities. Most of these diseases are rare disorders and the incidence of diseases is largely dependent on ethnic origin. For example, neonatal cholestasis caused by citrine deficiency is an important cause of cholestasis in East Asian children [30]. Alpha-1-antitrypsin deficiency and cystic fibrosis are important causes of cholestasis in Western countries (somewhat lower incidence in the Asian population). Congenital disorders of bile acid metabolism constitute a group of important metabolic disorders that cause cholestasis in infants. Neonatal hemochromatosis is an important cause of neonatal liver failure, which manifests as an early onset of cholestasis. However, recent studies have shown that this condition is a disorder of gestational autoimmune liver disease instead of hereditary hemochromatosis [31]. Other congenital abnormalities, such as chromosomal abnormalities, endocrine disorders, and developmental disorders can also cause cholestasis. Liver disease, as a rule, is a multiorgan manifestation of congenital anomalies.

Etiology of hereditary disorders of bilirubin metabolism causing indirect hyperbilirubinemia. Violations of bilirubin metabolism of hereditary genesis lead to its accumulation in the liver and blood, which is confirmed by a biochemical examination of blood serum and is clinically manifested by jaundice. Thus, it is known that Gilbert's syndrome is a benign clinical condition that is usually manifested by mild periodic jaundice in children or adults and is associated with a mutation of the UGT1A1*28 gene region [32]. Crigler-Najjar syndrome is also caused by

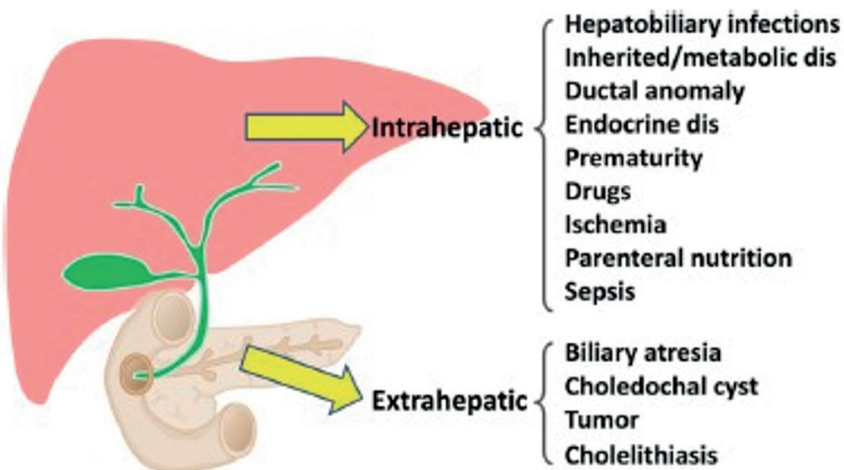

Fig. 2. Etiology of hereditary or secondary intrahepatic and extrahepatic cholestasis (H.L. Chen et al., 2018)

mutations in the UGT1A1 gene. Type I is a rare autosomal recessive disorder with complete loss of enzyme function that causes extremely high bilirubin levels (greater than 20 mg/dl) and can lead to encephalopathy due to jaundice. Genetic variations in the UGT1A1 gene, especially the 211 G to A mutation (G71R in exon 1), as well as variations in the glucose-6-phosphate dehydrogenase (G6PD) and OATP2 genes, also contribute to neonatal and breastfeeding jaundice [33]. A homozygous 211 G to A mutation has been reported to be associated with severe neonatal jaundice.

Etiology of hereditary cholestasis causing direct hyperbilirubinemia. Hereditary cholestatic liver diseases can manifest at an early stage of life. Over the past 20 years, tremendous progress has been made in understanding the genetic background of cholestatic liver disease. To date, more than 100 hereditary diseases have been identified that cause cholestatic liver diseases with primary manifestations in the form of jaundice. Some of them may be associated with congenital anomalies or damage to multiple organs. Thus, mutations of the BSEP, FIC1, MDR3 genes have been proven, and there are also reports of adaptive changes in hepatocyte transporters associated with obstructive cholestasis in biliary atresia, an important extrahepatic cholestatic liver disease with a common symptom of prolonged neonatal jaundice [34]. Progressive familial intrahepatic cholestasis (PFIC) is a clinical syndrome with signs of chronic intrahepatic cholestasis that usually begins in childhood and progresses to biliary cirrhosis and liver failure within 10-20 years of life [35]. The first three types of genetic defects identified are commonly called PFIC1, PFIC2, and PFIC3. Thus, PFIC1 and PFIC2 are characterized by low serum γ-glutamyltransferase (GGT) levels. Patients with PFIC1 (Byler disease) have mutations in the FIC1 gene, and patients with PFIC2 have a mutated BSEP gene. PFIC3 is characterized by high serum GGT levels and is caused by genetic mutations in the MDR3 gene [36]. At the same time, the BSEP gene plays a key role in bile physiology, as it regulates the export of bile salts and is the main driver of bile outflow [37]. Thanks to advances in genetic technology, new disease-causing genes for PFIC have been reported in recent years. Thus, the FXR gene is a key regulator of bile acid metabolism and is involved in a new form of childhood cholestasis with liver failure (a fatal case of childhood cholestasis with liver failure that occurred under the age of 3 months was identified) [38].

Dubin-Johnson and Rotor syndrome are hereditary disorders that are manifested by an increase in the content of direct bilirubin but with a normal or minimally increased level of AlT, which is clinically manifested by jaundice. Dubin-Johnson syndrome is a disease with an autosomal recessive type of inheritance. The genetic defect consists of the appearance of a mutation in the gene encoding a protein that is an ion channel, an organic anion transporter (cMOAT) and is characterized by a black color of the liver and pigment deposition in hepatocytes. Neonatal cholestasis caused by Dubin-Johnson syndrome has been reported in Taiwan and Japan [39]. Recently, it was established that Rotor syndrome is caused by a genetic disorder of both SLCO1B1 and SLCO1B3 genes [40]. These two disorders are benign and do not require special treatment.

Genetic cholestasis not only causes liver disease in children but can also be present in adults. In general, functional disorders of proteins are less harmful and are usually caused by multifactorial disorders. Cholestasis during pregnancy is associated with genetic variants/mutations in ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 genes [41]. Adult-onset benign recurrent intrahepatic cholestasis (BRIC) is also associated with genes associated with PFIC and may have mutations that are less harmful. Acquired forms of cholestasis, such as drug-induced liver disease, are also associated with genetic changes [42].

Diseases associated with the malformation of the ductal system are an important group of

developmental disorders that lead to insufficiency or malformation of the intrahepatic or interlobular bile ducts. Alagille syndrome is a congenital autosomal dominant family syndrome characterized by a combination of intrahepatic cholestasis, neonatal jaundice and hepatomegaly (enlargement of the liver), defects of the heart, skeleton, eyes and kidneys, and a characteristic facial appearance [43]. The syndrome has variable expression, patients have mutations in the JAG1 and Notch2 genes.

Surgical pathology and liver failure. It is important to remember that in surgical practice, liver dysfunction with transformation into ALF can develop during operations for gallstone disease, choledocholithiasis, obstructive jaundice, cholangitis, post-cholecystectomy syndrome, acute pancreatitis, malignant neoplasms of the biliary tract and pancreas [44]. Wide use of endoscopic interventions (papillotomy, stenting) and laparoscopic operations in the pathology of the pancreatico-biliary zone increases the share of iatrogenic complications associated with biliary tract patency disorders. Liver resections of different volumes are also dangerous for the development of ALF, in connection with the development of programs for preoperative preparation of this category of patients with planning for the development of possible postoperative consequences, their prevention and treatment [45].

In patients with a large and giant duodenal ulcer penetrating the hepatoduodenal ligament, as well as with juxtapapillary ulcers of the duodenum, mechanical cholestasis is a severe aggravating factor that requires the use of reconstructive surgical technologies [46].

At the same time, statistical data indicate that 25% of surgical patients have a heavy alcohol history with a risk of developing alcoholic delirium [47]. In particular, patients with acute abdominal pathology (peritonitis, acute calculous cholecystitis, complicated by choledocholithiasis, mechanical jaundice and cholangitis, pancreatic necrosis, blood loss with posthemorrhagic anemia, etc.) develop delirium of mixed genesis, which also provokes ALF.

Pathophysiological changes occurring in obstructive jaundice. Various cerebral, cardiovascular, pulmonary, and metabolic changes may occur during the course of obstructive jaundice. With ALF, there is a decrease in peripheral vascular resistance and blood pressure, which is due to hyperdynamic blood circulation with tachycardia and increased cardiac output. Non-cardiogenic pulmonary edema (acute respiratory distress syndrome), cerebral edema with increased intracranial pressure against the background of increased excretion of ammonia by nitrogenous substances in the intestines, changes in mental status (as a result of portosystemic encephalopathy) may also be observed. In the early stages of ALF, both metabolic and respiratory alkalosis most often develop. During the development of septic shock, metabolic acidosis occurs. Hypokalemia is often noted, and hypophosphatemia and hypomagnesemia may develop. Hypoglycemia occurs due to a decrease in glycogen reserves in the liver with disturbances in the processes of gluconeogenesis and destruction of insulin [48].

In general, obstructive jaundice can lead to various pathophysiological processes, including local effects on the liver parenchyma, bile ducts, and systemic manifestations. Under these conditions, patients with jaundice have a high risk of developing liver dysfunction, kidney failure, nutritional deficiency, tendency to bleed, weakened immunity, infections, and mortality in severe cases is 20-60%.

A complete understanding of the pathophysiology in patients with jaundice is crucial for implementing optimal preventive measures and improving outcomes (Fig. 3) [49].

Effect on the biliary duct system. Under physiological conditions, the pressure in the biliary tract varies from 5 to 10 cm H_2O, however, the violation of bile excretion leads to an increase in the pressure in the ducts, and in the case of an excess of 10-15 cm H_2O production of bile by the liver stops. Also, as a result of increased pressure in the ducts of the biliary

system, the risk of bile infection and the development of cholangitis increases [50]. Under these circumstances, the barrier function of the bile ducts is disturbed, which leads to an increase in their permeability and reflux of bile to the hepatic sinusoids, the entry of microorganisms and endotoxins into the general circulation, severe intoxication and sepsis [51]. Inflammatory infiltration of the portal sinuses by polymorphonuclear neutrophils with fibrin deposition and the appearance of necrotic foci in the liver parenchyma occurs. Systemic inflammatory response syndrome with secondary damage to hepatocytes progresses, dysfunction of vital organs occurs and ALF develops.

Effect on the structure of the liver. According to the data of experimental studies, in the case of obstructive jaundice, the contour of the liver changes due to the development of fibrosis, ductal hyperplasia, and the formation of an inflammatory infiltrate of the portal vein [52]. A liver biopsy reveals tubular cholestasis, changes in the portal vein in the form of its expansion, ductal hyperplasia, and neutrophilic infiltration. According to other data, lipid infiltration of the liver tissue is observed, indicating its oxidative damage, but after the obstruction is removed, there is an increase in the particles of indium oxide, tin and normal mitochondria, which reflects the regenerative function of the cellular structure of the liver and suggests that liver damage can be reversed [53]. It was also found that the main pathological characteristic of obstructive jaundice, which is caused by biliary atresia, is their hyperplasia with the participation of fibroblasts and various inflammatory cells [54]. In other studies (experiments on rats), damage to the epithelium of the bile ducts in the form of a violation of cell morphology, thickening of the basement membrane, edema in the interstitium, increased thickness and expansion of the bile duct was observed. Under these circumstances, irregular formations around liver cells, thickening of the fibrous membrane, and an increase in the distance between fibers were detected [55]. At the same time, it was found that hepatocyte apoptosis, endotoxemia, a decrease in the level of glutathione in the plasma and a rapid increase in the level of oxidized glutathione were observed in rats with obstructive jaundice, compared to the control group that received treatment. Subsequently, the tight junctions of hepatocyte structures were destroyed, and oral administration of Lactobacillus plantarum helped to restore the barrier function of the liver [56].

Also, it should be noted that under the

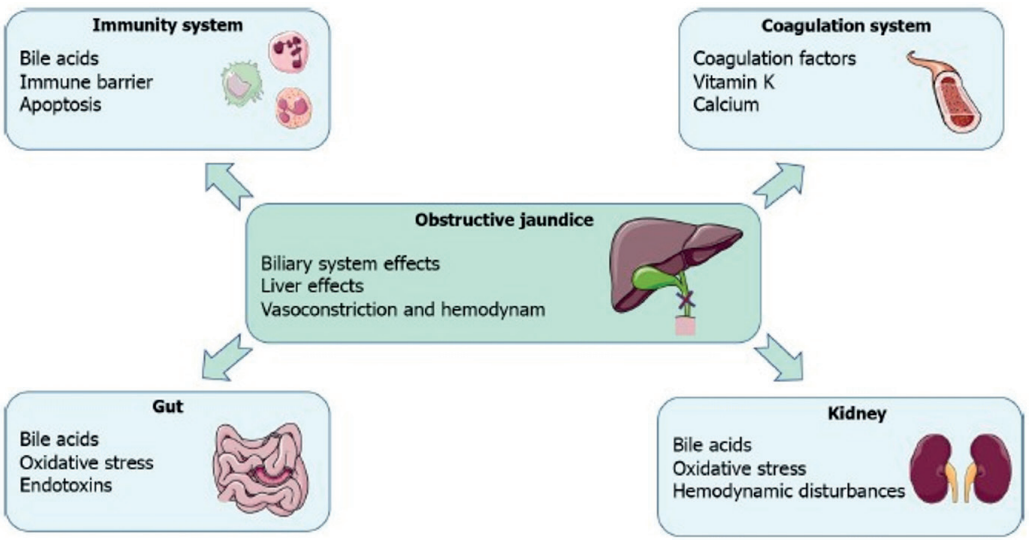

Fig. 3. Pathophysiological consequences of obstructive jaundice (J.J.Liu, et al, 2023)

conditions of obstructive jaundice, endothelial cells of the hepatic sinuses are damaged, which makes the liver more susceptible to ischemia-reperfusion, reduces vasoconstrictor tension, and reduces vasoreactivity. Reactive oxygen species (ROS) play an important role in the pathogenesis of jaundice because they reduce the bioavailability of nitric oxide, thereby impairing vasodilation and endothelial cell growth, causing oxidative damage that can lead to atherosclerosis [57].

The presence of portosystemic venous shunts in obstructive jaundice increases the entry of endotoxins into the systemic bloodstream [58]. Thus, endotoxins (lipopolysaccharides) are components of the cell walls of gram-negative bacteria. Small amounts of endotoxins are produced in the gut under normal conditions, and the liver is a central immunological organ that is particularly rich in innate immune cells and constantly exposed to circulating nutrients and endotoxins derived from the gut microbiota [59]. At the same time, endotoxins can enter the systemic bloodstream, damaging Kupffer cells. During obstructive jaundice, insufficient outflow of bile and other factors that contribute to the absorption of endotoxins from the portal system and disruption of reticuloendothelial function contribute to the development of systemic endotoxemia. Intestinal obstruction, after bile enters the intestine, leads to abnormal proliferation of the microflora, leading to intestinal mucosal barrier damage, bacterial translocation, and ultimately increased endotoxin absorption [60]. Once in the bloodstream, these products cause organ damage by stimulating various cells (monocytes, macrophages, granulocytes, and endothelial cells) to produce cytokines (tumor necrosis factor (TNF), platelet-activating factor, interleukin (IL), oxygen radicals, prostaglandins (Pg), and procoagulants). This explains the frequent development of complications in patients with obstructive jaundice in the postoperative period (purulent-septic complications, gastrointestinal bleeding, renal failure, suture failure, and multiple organ failure).

Effect on the blood coagulation system. It has been proven that patients with obstructive jaundice have a higher risk of developing thromboembolic complications [61]. Thus, hypercoagulation phenomena are observed in this category of patients, namely, it was found that the coagulation index is associated with an increase in the concentration of direct bilirubin, but the tendency to hypercoagulation is independent of the prothrombin time (PTT), which is associated with increased activity of fibrin polymers on platelet membranes [62]. In addition, obstructive jaundice can lead to acquired disorders of the blood coagulation system, the basis of which is insufficient secretion of bile salts, which leads to malabsorption of vitamin K, insufficient synthesis of coagulation factors, inability to clear coagulation products and activation of fibrinolysis, and as a result - the development of disseminated intravascular syndrome blood clotting Vitamin K deficiency may be the cause of hemorrhagic diathesis even with normal laboratory parameters such as PTT and INR. In addition, malabsorption of vitamin D and lipids can lead to their deficiency, which leads to a decrease in calcium content [63].

Effect on kidneys. Acute kidney injury is diagnosed in almost 50% of patients with ALF. Since the level of blood urea nitrogen concentration depends on the synthetic function of the liver, it cannot objectively reflect the function of the kidneys, so the determination of the creatinine level is a more objective method. According to the literature, 49% of patients with hepatoportal cholangiocarcinoma (HCCA) associated with obstructive jaundice develop acute renal failure. Other studies indicate that the incidence of this complication can vary from 5% to 16%, and the mortality rate is 70-80% [64]. Under these circumstances, kidney damage occurs as a result of the preferential excretion of bile acids by the urinary system due to obstruction of the bile ducts (bile acids cause damage to the epithelium of the renal tubules) [65]. In addition, renal failure can also

be caused by intestinal endotoxemia, which affects various body functions, including the coagulation system, hemodynamic balance, inflammation, and oxidative damage [66]. Thus, hemodynamic disturbances may occur as a result of impaired liver function and kidney damage. The liver plays a key role in maintaining normal blood flow and pressure, and damage to it can cause changes in these parameters. Under these circumstances, renal hemodynamic disturbances are the main mechanisms underlying acute renal failure against the background of obstructive jaundice. The renin-angiotensin-aldosterone system (RAAS) is a key player in the progression of kidney disease. Inhibition of renin and aldosterone, which blocks the RAAS, is an effective way to prevent acute renal failure due to obstructive jaundice [67]. Experiments on rats with acute renal failure on the background of obstructive jaundice were also published, in which an increase in the secretion of prostaglandin E2 (Pg E2) in the urine was found. At the same time, in the control group of rodents with a creatinine clearance lower than average, less Pg E2 was excreted in the urine. This indicates that Pg E2 may play a protective role and prevent deterioration of renal function [68]. A certain place is also given to oxidative stress, which occurs as a result of an imbalance between the oxidizing and antioxidant systems, when the body is exposed to the accumulation of numerous harmful factors, such as drugs, toxic metabolites, cholestasis, and alcohol metabolism products. A number of studies indicate a connection between the occurrence of renal failure on the background of obstructive jaundice with the content of cholesterol, malondialdehyde, superoxide dismutase, and other free oxygen radicals [69].

Effect on the immune system. First of all, it should be noted that bile affects the homing and distribution of T-lymphocytes in the intestinal lymphoid tissue, and its absence in the intestinal lumen leads to a decrease in the number of CD4- and CD8- T-lymphocytes and cells expressing mucosal cell adhesion molecule 1 in its own plate [70]. The effect of bile on the size and number of B-lymphocytes in Peyer's patches has been proven (in the absence of bile in the lumen of the intestine, apoptosis of B-lymphocytes is induced). Bile also contains immunoglobulin A, which enhances mucosal defenses or binds to bacteria and viruses, which is necessary to support the functioning of the local immune barrier in the intestine. The occurrence of immune system dysfunction increases the risk of translocation of intestinal bacteria and the occurrence of systemic inflammatory response syndrome. In turn, an increase in the content of bile acids in the blood leads to damage to macrophages and Kupffer cells, thereby disrupting the functions of the liver and systemic immunity and accelerating the development of sepsis in patients with obstructive jaundice [71].

Effect on intestines and intestinal barrier. Under physiological conditions, bile has an anti-inflammatory function, and freely enters the intestinal lumen through the bile ducts, which helps remove bacteria and prevents their migration from the small intestine to the common bile duct. In the case of obstructive jaundice, phenomena of cholestasis occur, the multiplication of bacteria in the intestines, an increase in the content of bile acids in the blood serum, damage to the epithelium of the intestinal mucosa by products of oxidative stress, destruction of the tight junctions of the intestines and a decrease in the expression of the protein of the tight junction of the small intestine. Ultimately, these changes lead to the destruction of the intestinal tissue structure and the disintegration of the barrier function of the intestinal mucosa, which leads to the penetration of endotoxins and bacteria into the systemic bloodstream [72].

Microbial translocation. As mentioned above, the absence of bile in the intestines is accompanied by dysbacteriosis, which causes damage to the protective barrier of the intestinal mucosa, the translocation of bacteria and their toxins to the general circulation and an increase in endogenous intoxication. Endotoxins damage the membranes of highly differentiated

organ-specific cells of vital organs, stimulating monocytes, macrophages, granulocytes, and endothelial cells to produce cytokines, such as TNF, platelet activation factor, proinflammatory interleukins, oxygen radicals, prostaglandins, and procoagulants (Fig. 4) [73].

Under these circumstances, bacterial translocation leads to acceleration of the occurrence and progression of ALF. Consequently, ALF is a progressive condition that requires constant monitoring, predicting outcomes and offering treatment options, as observed in other pathologies, is extremely difficult, and the mortality rate can reach 40-50% [74]. However, there is a so-called «golden window of opportunity», that is, the effective use of therapy in the first week of the disease shows better clinical results. Therefore, the first week from the onset of symptoms is very important and is usually accompanied by a systemic inflammatory response syndrome, which has significant consequences. At the same time, the main factors influencing the results of treatment of patients at different points in time are the combination of the critical functional reserve of the liver and the nature and severity of liver damage. As soon as the systemic inflammatory response syndrome develops, there is a further increase in inflammation, which is systemic in nature and leads to the failure of other organs. Therefore, this period before the development of immune paralysis and subsequent development of sepsis is considered a «golden window of opportunity». Under these circumstances, understanding the pathophysiological features of the course of ALF makes it possible to carry out the necessary diagnostic measures in a timely manner and to offer the appropriate and adequate therapy.

CONCLUSION

Acute liver failure is a syndrome that occurs in 20-59% of patients with liver pathology and is one of the main causes of death in 40% of patients with mechanical jaundice of benign origin and in more than 70% of cases of tumor obstruction of the biliary tract. One of the main factors in the development of acute liver failure is a violation of the patency of the biliary tract (cholestasis), both of benign and malignant origin (7:3). The pathogenesis of acute liver failure caused by cholestasis is based on the damage and death of hepatocytes due to impaired blood circulation in the liver, as well as the toxic effect on the parenchyma of both the etiological factors themselves and their metabolites. Understanding

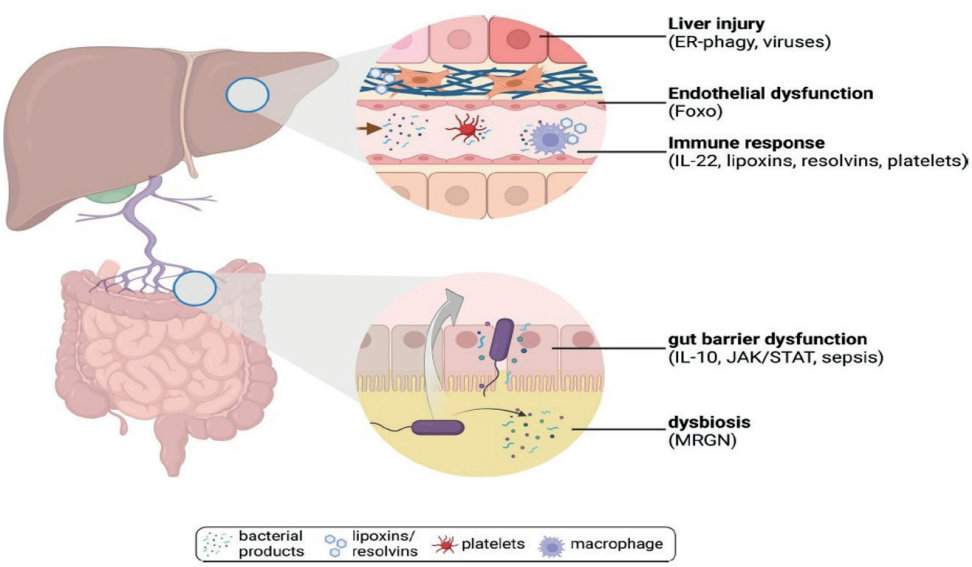

Fig. 4. Potential mechanisms and triggers of acute liver failure (R. Schierwagen et al., 2023)

the pathophysiological aspects of the course of acute liver failure makes it possible to carry out the necessary diagnostic measures and apply the appropriate therapy in a timely manner.

Financing. The *work was performed in accordance with the plan of research work of the Department of Surgery No. 2 of Bogomolets National Medical University: "Development and implementation of methods of diagnosis and treatment of acute and chronic surgical pathology of abdominal organs". The authors did not receive additional financial support.*

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ПАТОФІЗІОЛОГІЧНІ ОСОБЛИВОСТІ ГОСТРОЇ ПЕЧІНКОВОЇ НЕДОСТАТНОСТІ, СПРИЧИНЕНОЇ ХОЛЕСТАЗОМ

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Гостра печінкова недостатність це синдром, що зустрічається у 20--59% пацієнтів з патологією печінки та є однією з основних причин смерті 40% хворих з механічною жовтяницею доброякісного походження та більш ніж у 70% пацієнтів з пухлинною обструкцією жовчовивідних шляхів та головки підшлункової залози. Здебільшого він є наслідком гострого ушкодження печінки (вірусного або медикаментозного), проте може виникнути при довготривалій обструктивній жовтяниці, бути першим проявом хвороби Вільсона, аутоімунного хронічного гепатиту, суперінфекції вірусу гепатиту Д на тлі хронічного гепатиту В. Метою роботи було дослідження патофізіологічних особливостей розвитку гострої печінкової недостатності у пацієнтів з порушеннями відтоку жовчі. В основі патогенезу гострої печінкової недостатності, викликаної холестазом, лежить ушкодження та загибель гепатоцитів внаслідок порушення циркуляції крові в печінці, а також токсичний вплив на паренхіму як самих етіологічних чинників, так і їх метаболітів. Перший тиждень від початку проявів симптомів дуже важливий і зазвичай супроводжується синдромом системної запальної відповіді, який має суттєві наслідки. Водночас основними факторами, що впливають на результати лікування пацієнтів у різні моменти часу є поєднання критичного функціонального резерву печінки та тяжкості її ураження. У разі розвитку синдрому системної запальної відповіді відбувається подальше посилення запалення, що носить системний характер та призводить до виникнення недостатності інших органів. За цих обставин розуміння патофізіологічних особливостей перебігу гострої печінкової недостатності дає можливість своєчасно провести діагностичні заходи та запропонувати відповідну терапію.

Ключові слова: гостра печінкова недостатність; холестаз; цироз; гепатит; рак підшлункової залози.

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Received 10.02.2024