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Clinical Guidelines of the Russian Society for the Study of the Liver, Russian Gastroenterological Association, Russian Society for the Prevention of Non-Communicable Diseases, Russian Association of Endocrinologists, Russian Scientific Medical Society of Therapists, National Society of Preventive Cardiology, Russian Association of Gerontologists and Geriatricians on Drug-Induced Liver Injury

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Aim. The clinical guidelines are intended to provide information support for making decisions by gastroenterologists, general practitioners and internists that will improve the quality of medical care for patients with drug-induced liver injury, taking into account the latest clinical data and principles of evidence-based medicine.

Key points. Clinical guidelines contain information about current views on etiology, risk factors and pathogenesis of drug-induced liver injury, peculiarities of its clinical course. Also, the recommendations provide information on current methods of laboratory and instrumental diagnostics, invasive and non-invasive tools for drug-induced liver injury disease and its clinical phenotypes assessment; approaches to its treatment, considering the presence of comorbidities, features of dispensary monitoring and prophylaxis. The information is illustrated with algorithms of differential diagnosis and physician's actions. In addition, there is information for the patient and criteria for assessing the quality of medical care.

Conclusion. Awareness of specialists in the issues of diagnosis, treatment and follow-up of patients with drug-induced liver injury contributes to the timely diagnosis and initiation of treatment, which in the long term will significantly affect their prognosis and quality of life.

Keywords: hepatotoxicity, drug-induced autoimmune-like hepatitis, liver injury, acute liver failure, hepatic encephalopathy, liver panel, liver steatosis, steatohepatitis, dyslipidemia, fatty liver disease, cardiometabolic risk factors, nonalcoholic steatohepatitis

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Клинические рекомендации Российского общества по изучению печени, Российской гастроэнтерологической ассоциации, Российского научного медицинского общества терапевтов, Российского общества профилактики неинфекционных заболеваний, Российского научного медицинского общества терапевтов, Российского общества клинической онкологии, Научного сообщества по изучению микробиома человека по лекарственным поражениям печени

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Цель представления: клинических рекомендаций заключается в обеспечении информационной поддержки для принятия врачами-гастроэнтерологами, врачами общей практики и врачами-терапевтами решений, способствующих повышению качества оказания медицинской помощи пациенту с лекарственными поражениями печени, с учетом новейших клинических данных и принципов доказательной медицины.
Основное содержание. Клинические рекомендации содержат информацию о современных представлениях об этиологии, факторах риска и патогенезе лекарственных поражений печени, особенностях их клинического течения. Также в рекомендациях представлена информация об актуальных методах лабораторной и инструментальной, инвазивной и неинвазивной диагностики лекарственных поражений печени и их клинических фенотипов, подходах к их лечению с учетом наличия коморбидностей, особенностей диспансерного наблюдения и профилактики. Приведенная информация проиллюстрирована алгоритмами дифференциального диагноза, действий врача. Помимо этого, присутствует информация для пациента и критерии оценки качества оказания медицинской помощи.
Заключение. Осведомленность специалистов в вопросах диагностики, лечения и наблюдения пациентов с лекарственными поражениями печени способствует своевременной постановке диагноза и инициации лечения, что в отдаленной перспективе будет существенно влиять на их прогноз и качество жизни.
Ключевые слова: гепатотоксичность, лекарственно-индуцированный аутоиммуноподобный гепатит, поражение печени, острая печеночная недостаточность, печеночная энцефалопатия, печеночная панель, стеатоз печени, стеатогепатит, дислипидемии, жировая болезнь печени, кардиометаболические факторы риска, неалкогольный стеатогепатит
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Terms and definitions

Asymptomatic increase in transaminases is a transient increase in ALT and AST in response to the administering of a new drug, not accompanied by other signs of liver damage, representing an adaptive reaction.

Hepatotoxicity is liver damage caused by foreign substances (xenobiotics), a particular case of which is drug-induced liver injury.

Hy's Law is a prognostic rule formulated by Hy Zimmerman for hepatocellular DILI: an increase in ALT activity > 3 ULN with jaundice (an increase in bilirubin level over 42 umol/L) determines a high (10 % of cases or more) risk of developing acute liver failure with a fatal outcome.

Immune checkpoint inhibitors (ICI) are a class of antitumor drugs (monoclonal antibodies) that target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) ipilimumab** and others, programmed cell death receptor 1 (PD-1) nivolumab**, pembrolizumab** and others and its ligand (PD-L1) (belong to the ATX group: PD-1/PDL-1 (programmed cell death protein 1/programmed death ligand 1) inhibitors, lymphocyte activating gene-3 (*LAG-3*).

Immune-mediated adverse reaction is a side effect caused by excessive activation of the immune system during antitumor immunotherapy.

Clinical trial is any study conducted with the participation of a human subject to identify or confirm the clinical and/or pharmacological effects of the study products and/or to identify adverse reactions to the study products and/or to study their absorption, distribution, metabolism and excretion in order to evaluate their safety and/or efficacy.

***R* coefficient** is the ratio of serum ALT/ALT-ULN activity divided by the ratio of serum ALP/ALP-ULN activity. A value of $R \geq 5$ identifies the

hepatocellular type of liver injury, while a value of $R \leq 2$ classifies the cholestatic type of liver injury, and a value of $5 > R > 2$ reflects the mixed type of DILI.

Medication is a substance or mixture of substances used for the prevention, diagnosis, treatment of diseases or modification of physiological functions of the body.

Drug-induced liver injury is liver damage caused by any drug, including small synthetic molecules, biologics, herbal products, herbal and dietary supplements.

Drug interaction is a phenomenon in which the simultaneous use of two or more drugs produces an effect that differs from the effect of each of them individually.

Drug-induced autoimmune-like hepatitis is a liver disease caused by taking medications and mimicking classical autoimmune hepatitis.

Medical rehabilitation is a set of medical and psychological procedures, aimed at the full or partial restoration of impaired and/or compensation for lost functions of an affected organ or body system, maintaining body functions during the completion of an acutely developed pathological process or exacerbation of a chronic pathological process, as well as the prevention, early diagnosis and correction of possible dysfunctions of damaged organs or body systems, prevention and reduction of the degree of possible disability, quality of life improvement, preservation of the patient's ability to work and his social integration into society.

Adverse reaction is an unintended, unfavorable reaction of the organism that may be associated with taking a medication

Acute liver failure is a rapid (less than 26 weeks) and sudden impairment of liver function with the development of hypocoagulation (INR > 1.5) and hepatic encephalopathy in a patient without pre-existing liver disease.

Hepatic encephalopathy is a complex of potentially reversible neuropsychiatric disorders that arise as a result of liver failure and/or portosystemic shunting of blood.

Liver tests or liver panel are blood biochemistry parameters that include ALT, AST, ALP, GGT, bilirubin, albumin and reflect inflammation, cholestasis, synthetic function.

Patient is an individual who is receiving medical care or who has applied for medical care, regardless of the presence of an illness or condition.

Suspected drug is a substance or mixture of substances for the prevention, diagnosis, treatment of diseases or changes in the physiological functions of the body, the use of which is associated with the development of drug-induced liver injury.

Causative drug is a substance or mixture of substances for the prevention, diagnosis, treatment of diseases or changes in the physiological functions of the body, the use of which led to the development of drug-induced liver injury.

Clinical Guidelines Development/Update Working Group is a group of specialists who work together and in a coordinated manner to develop/update clinical guidelines and who bear overall responsibility for the results of this work.

Syndrome is a stable set of symptoms with a single pathogenesis.

Condition — changes in the body that occur due to the influence of pathogenic and (or) physiological factors and require medical care.

Mean baseline transaminase values are the mean ALT and AST levels that a patient with underlying liver disease had when drug-induced liver injury developed.

Liver steatosis is an accumulation of fat in the liver, in which lipid accumulation occurs in more than 5 % of hepatocytes.

Steatohepatitis is an accumulation of fat in the liver, accompanied by intralobular inflammation, ballooning degeneration of hepatocytes and the possible development of fibrosis.

Liver transplantation is a surgical procedure, that involves replacing a damaged liver with a whole liver or a part of healthy liver obtained from another person, called a donor.

Severe liver disease is a general term for various conditions in which the liver is significantly damaged and unable to perform its functions.

Level of evidence is the degree of confidence that the effect obtained from the use of a medical intervention is true.

Grade of recommendation is the degree of confidence in the effectiveness of an intervention and that following the recommendation will bring more benefit than harm in a particular situation.

Phenomenon of adaptation (tolerance) is a decrease in the reaction of organism to repeated administration of a drug.

Pharmacodynamics is a section of pharmacology that studies the localization, mechanism of action and pharmacological effects of drugs, the strength and duration of their action.

Pharmacokinetics is a branch of pharmacology that studies how the body absorbs, distributes, metabolizes, and excretes drugs after administration. It describes the processes that occur with drugs in organism, how quickly and in what quantities they enter the blood and tissues, and how long they remain in organism.

Pre-existing liver disease is a liver disease that precedes another liver disease and may influence its course and prognosis.

1. Brief information on a disease or condition (group of diseases or conditions)

1.1. Definition of a disease or condition (group of diseases or conditions)

Drug-induced liver injury (DILI) is a liver damage caused by any drug, including small synthetic molecules, biologics, herbal products and dietary supplements. Damaging agents can target hepatocytes, cholangiocytes, stellate cells, and the sinusoidal endothelium [1, 2].

In Russian-language literature, the term "ЛППП" (could be translated from Russian as Liver Damage due to Medication) is mostly used. The term "drug-induced liver injury" used in English-language literature ("DILI" ("ЛИППП" in Russian)) is less common in in Russian-language literature [1, 2].

1.2. Etiology and pathogenesis of a disease or condition (group of diseases or conditions)

Etiology

DILI can be caused by a wide range of medications, herbal products and dietary supplements. Various databases on adverse drug reactions, including DILI, exist:

- WHO database VigiBase® (www.who-umc.org);
- European Medicines Agency Database (http://www.adrreports.eu/en/search.html);
- Lareb Pharmacovigilance Centre, The Netherlands (https://www.lareb.nl/en/databank/);
- Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddra.org/);
- Drug-Induced Liver Injury Network (DILIN), Food and Drug Administration (FDA) (https://dilin.org/);
- The Liver Toxicity Knowledge Base (LTKB), FDA (https://www.fda.gov/science-research/liver-toxicity-knowledge) etc. LiverTox, the DILIN registry (https://www.ncbi.nlm.nih.gov/books/NBK547852/), which includes prescription and over-the-counter drugs, a detailed description of the DILI, that they cause (epidemiological data, mechanism of hepatotoxicity, clinical features etc.), is a convenient information resource. Another database, DILIrank, allows to assess the potential of particular drugs to cause DILI and predicts the potential severity of DILI. It currently includes 1,036 drugs (https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset). Currently it includes 1036 drugs.

Pathogenesis

DILI develops through various pathogenetic mechanisms (Table 1), which include:

- Direct, caused by drugs with a direct and predictable dose-dependent effect. This type of damage is most common and can be reproduced in animal models. It typically develops upon reaching high therapeutic or higher doses (specific values may vary for different individuals) after a short latency (1–5 days).
- Idiosyncratic, characteristic of drugs that do not initially have hepatotoxic potential and are not dose dependent. The toxic effect is unpredictable, individual, not reproducible in an animal model, and is usually due to the patient's genetic characteristics. Latency is variable and can last from several days to several months, in some cases, years [3].
- Indirect (mediated) is damage to the liver that is not caused by the direct effect of drug on the organ but develops indirectly (secondarily to the effect of drug on immune response, metabolic processes, other organs and systems, etc.) [4, 5].

Risk factors for DILI

There are no universal risk factors for the development of DILI; they vary depending on the drug used (see also Table 4 in Appendix A3, Section 5.1.1 "Primary Prevention of DILI").

The following are considered risk factors for the development of DILI.

I. Patient-related factors

- *Age.* Older adults are more susceptible to DILI due to age-related changes in drug metabolism and liver function [6]. The risk of DILI increases with age due to the use of certain medications, such as isoniazid**, amoxicillin + clavulanic acid**, and nitrofurantoin [7]. From a practical perspective, age as a risk factor is important in predicting specific types and phenotypes of DILI. Cholestatic and chronic DILI are more common in older individuals [8, 9]. Conversely, hepatocellular DILI is more common in younger individuals, and the risk of DILI is higher due to valproic acid**, nonsteroidal anti-inflammatory and antirheumatic drugs (NSAIDs) [8–10].
- *Gender.* It is believed that women suffer from DILI more often than men, possibly due to hormonal differences and the peculiarities of metabolism of some drugs, but there is no convincing evidence to support this statement. Female gender may be an independent risk factor for the hepatocellular phenotype of DILI with the development of fulminant liver failure (women account for 77–89 %) [11, 12].

Table 1. Mechanisms of DILI (modified from CIOMS (2020)) [4, 5]

Parameters	Direct (hepatotoxic damage)	Idiosyncratic lesion	Indirect (mediated)
Rate of occurrence	High	Low	Intermediate
Dose-related	+	–	–
Predictable	+	–	Occasionally
Reproducibility	+	–	Occasionally
Latency	Fast (days)	Variable (days to months)	Typically delayed (weeks to months)
Implicated drugs (examples)	Paracetamol**, Methotrexate**,	Amoxicillin-clavulanate**, other beta-lactam antibacterial medications (cephalosporins), isoniazid**, nitrofurantoin	Immune checkpoint inhibitors, monoclonal antibodies (anti-CD20), protein kinase inhibitors
Pathologic mechanisms	Dose-dependent hepatotoxicity	Idiosyncratic metabolic or immune response of the host	Indirect effects on the liver or immunity of the host

• *Malnutrition/obesity* [13]. For example, obesity increases the risk of liver damage when using halothane**, and tamoxifen** is a trigger for the development of steatohepatitis and liver fibrosis. The hepatotoxicity of isoniazid** and paracetamol** increases with fasting [14].

• *Genetic predisposition plays* a significant role in idiosyncratic DILI. Some mutations may play a major role in their development if the gene product is crucial for drug metabolism. However, more often there is polygenic susceptibility associated with the influence of genetic factors on the immune response, mitochondrial function, etc. [15]. It has been proven that some genetic variants increase the risk of developing DILI. The PTPN22 rs2476601 polymorphism is a genetic risk factor for many drugs and major ethnic groups, probably due to its effect on the immune response [16]. Associations with HLA have been described for the hepatotoxicity of a number of drugs. Thus, predisposition to amoxicillin-clavulanate-induced DILI is determined by the DRB1*1501-DRB5*0101-DQB1*0602 haplotype [17]. A number of non-HLA associations have been identified, for example, polymorphisms in the N-acetyltransferase 2 gene are a risk factor for isoniazid-induced DILI** [18, 19].

• *Liver disease.* Certain liver diseases may be risk factors for the development of DILI associated with certain drugs. For example, viral hepatitis is a risk factor for isoniazid-associated DILI**, and non-alcoholic fatty liver disease (NAFLD) is a risk factor for tamoxifen-associated DILI**. Furthermore, underlying liver disease may worsen the course and prognosis of DILI associated with the development of DILI. Detailed information on this topic should be found in the instructions for use of the drug and in DILI databases.

• *Extrahepatic diseases.* Existing somatic diseases may be associated with the risk of DILI or worsen their prognosis. For example, in patients with diabetes, the severity of DILI increases with the use of anti-tuberculosis drugs. Diabetes mellitus is associated with the risk of death or liver transplantation (LT) [13, 20].

• *History of DILI.* Repeated use of the causative or suspected medication or its analogue should be avoided, since the severity of a recurrent reaction may be greater than the initial one. Some DILIs are characterized by cross-reactions with other drugs.

• *Alcohol.* Alcohol consumption is a risk factor for DILI with certain medications. Chronic alcohol abuse contributes to the development of hepatotoxic reactions at lower doses of some drugs, significantly increases their severity when using paracetamol**, isoniazid** is associated with DILI caused by anabolic steroids [21, 22]. However, alcohol abuse does not appear to be associated with the risk of severe outcomes in idiosyncratic DILI [22].

• *Tobacco smoking* induces an increase in the activity of enzymes involved in the biotransformation of drugs, in particular CYP1A2, and is therefore discussed as a possible risk factor for DILI [10]. However, the significance of tobacco

smoking for the development of DILI has not been proven. At the same time, there are descriptions of cases where smoking electronic cigarettes in itself can cause severe liver damage [23].

II. Factors directly related to drugs

• *Chemical structure, molecular weight, lipophilicity.* Drugs with a high molecular weight or high lipophilicity are generally more actively retained in the liver and have a more pronounced potential to induce hepatotoxicity [24, 25].

• *Daily dose of the drug.* Taking this parameter into account is important both for drugs that are characterized by clear dose-dependent hepatotoxicity (for example, paracetamol**), and for drugs that can cause idiosyncratic reactions (it is believed that at a dose of less than 50–100 mg daily, the risk of an idiosyncratic hepatotoxic reaction is lower than when using higher doses) [26, 27].

• *Pharmacodynamics* (*features of interaction with the biosubstrate*). Some drugs are capable of directly damaging key metabolic pathways in liver cells, causing disruption of their functions (for example, paracetamol**, valproic acid**, amiodarone**, etc.) [28, 29].

• *Pharmacokinetics* (*half-life, formation of active metabolites, haptenization*). The peculiarities of drug passage through metabolic transformation pathways can lead to the formation of toxic metabolites that can cause liver damage. Most often, this mechanism is realized with the participation of cytochrome P450 (e.g., CYP3A4, etc.), as well as through the haptenization mechanism, leading to the induction of a lymphocyte-mediated immune response. In this case, the duration of exposure to the drug or its metabolite is of great importance. The more active (more than 50 %) the drug metabolism in the liver, the higher the correlation found with an increase in alanine aminotransferase (ALT), the risk of liver failure and death [24, 30].

• *Drug class effect, cross-reactivity.* Given that the chemical structure of a drug significantly influences the risk and nature of DILI, certain manifestations of hepatotoxicity can be expected within similar chemical classes (e.g., HMG-CoA reductase inhibitors (statins), phenothiazine derivatives, etc.). [31].

• *Drug interactions* (a combination of two or more potentially hepatotoxic drugs increases the risk of DILI by 6 times [32]).

1.3. Epidemiology of a disease or condition (group of diseases or conditions)

Estimating the prevalence of DILI is difficult due to differences in reporting across countries, the variety of methods for assessing epidemiological data, insufficient alertness among physicians, and the difficulty in accurately determining the causes of liver damage.

Difficulties in identifying and diagnosing DILI are also associated with the nonspecificity of their symptoms, variable timing of onset, underlying and/or comorbid conditions and/or complications, and potential polypharmacy. Furthermore, it is important to consider other factors that hinder the assessment of the prevalence of DILI: possible reluctance on the part of patients to report the use of certain medications (antidepressants, antipsychotics (neuroleptics), erectile dysfunction medications, etc.) and physicians to document iatrogenic diseases; misinterpretation of the highly diverse symptoms; and the insufficient number of large-scale studies on this issue. Furthermore, predominantly severe liver damage is recorded, which is accompanied by an underreporting of mild forms of DILI.

According to various estimates, the incidence of DILI in the general population in developed countries is 3–19 per 100,000 people per year; according to other data, it is 3–6 % of all cases of drug use [33–35]. The prevalence of DILI among hospitalized patients is 1.4–4.4 % [33, 36, 37].

According to a meta-analysis (2022), the overall incidence of DILI worldwide is 4.94 per 100,000 person-years (95 % confidence interval (CI): 4.05–5.83) [6]. The incidence of DILI varies across regions: in Asia it is 17.82 per 100,000 person-years (95 % CI: 6.26–29.38), and in North America it is 1.72 per 100,000 person-years (95 % CI: 0.48–2.95). However, for the reasons described earlier, these figures are most likely significantly underestimated.

DILI is one of the main causes of acute liver failure (ALF) in developed countries, such as the United States and Western Europe [38]. Worldwide, there has been an increase in DILI due to the use of herbal products and dietary supplements (up to 25–50 % of DILI cases), which is most likely due to their wide availability, active advertising, the ability to purchase without a prescription and use independently in various combinations, as well as the often erroneous idea of the naturalness and safety of these drugs [39–41]. In addition, the development and implementation of new treatment methods, including malignant neoplasms, can expectedly lead to an increase in the number of cases of DILI. In different countries and regions, the list of drugs that cause DILI may differ due to the peculiarities of drug prescription and the predominant use of different dietary and herbal supplements.

In the Russian Federation, acute DILI is recorded in 2.7 % of hospitalized patients, but there is no comprehensive and accurate epidemiological data available [42]. This is due to the lack of a

national DILI registry and systematic data collection on cases, causes, and outcomes. In the Russian Federation, Roszdravnadzor oversees drug circulation and safety (https://roszdravnadzor.gov.ru/).

1.4. Features of coding a disease or condition (group of diseases or conditions) according to the International Statistical Classification of Diseases and Health Related Problems

K71. Toxic liver injury. Includes: drug-induced idiosyncratic (unpredictable) liver disease; toxic (predictable) liver disease.

If necessary to identify the toxic substance, use an additional code for external causes (Class XX):
K71.0 Toxic liver disease with cholestasis.

K71.1 Toxic liver disease with hepatic necrosis.

K71.2 Toxic liver disease with acute hepatitis.

K71.3 Toxic liver disease with chronic persistent hepatitis.

K71.4 Toxic liver disease with chronic lobular hepatitis.

K71.5 Toxic liver disease with chronic active hepatitis.

K71.6 Toxic liver disease with hepatitis features, not elsewhere classified.

K71.7 Toxic liver disease with liver fibrosis and cirrhosis of liver.

K71.8 Toxic liver disease with other disorders of liver.

K71.9 Toxic liver disease, unspecified.

1.5. Classification of a disease or condition (group of diseases or conditions)

1.5.1. Classification of DILI by the underlying mechanism of liver damage

DILI are divided into (Table 1):

- direct,
- idiosyncratic,
- indirect (see Section 1.2 "Etiology and pathogenesis of a disease or condition (group of diseases or conditions)").

1.5.2. Laboratory (biochemical) types (patterns) of drug-induced liver injury

Drugs and their metabolites affect various target cells (hepatocytes, cholangiocytes, stellate cells, sinusoidal endothelium) and liver structures, which is reflected in increased activity of various enzymes. Based on this, three laboratory patterns of DILI are distinguished depending on the predominance of increased ALT or alkaline phosphatase (ALP) activity:

- hepatocellular,
- cholestatic,
- mixed.

To determine the type of DILI, the R-value (R-value) is used — the ratio of ALT activity (multiple of the upper limit of normal (ULN)) and alkaline phosphatase (multiple of the ULN). (Determination of the pattern of DILI is described in detail in Section 2.3.1 "Basic laboratory diagnostic tests").

Based on the laboratory pattern of DILI, diagnostic approach is determined, and with this taken into account, causality is established and the prognosis is assessed (see Section 2) [2, 43].

1.5.3. Classification of DILI by duration

Depending on the duration of laboratory and/or instrumental and/or clinical signs of liver damage, a distinction is made between acute and chronic DILI. Chronic DILI does not necessarily indicate progressive liver damage but rather implies long-term persistence of changes in liver function after drug exposure. Various timeframes for establishing a diagnosis of chronic DILI are discussed, as liver fibrosis can develop as early as 3 months after the onset of hepatocellular DILI, while cholestatic DILI typically resolves slowly. Most hepatological associations propose the following time criteria:

- acute DILI (if changes in the liver persist for less than 3 months for the hepatocellular pattern and less than 6 months for the cholestatic pattern);
- persistent DILI (if changes in the liver persist for more than 3 months in the case of hepatocellular DILI and more than 6 months in the case of cholestatic DILI);
- chronic DILI with changes persisting for more than 1 year [13, 44].

1.5.4. DILI phenotypes

DILI is typically divided into phenotypes based on clinical, laboratory, instrumental, and, in some cases, morphological data. DILI phenotypes are quite diverse and can mimic virtually any type of acute or chronic liver disease. Some are associated with life-threatening outcomes and extremely poor prognosis (e.g., acute liver failure (ALF), vanishing bile duct syndrome (VBDS), liver cirrhosis (LC), and decompensation of pre-existing LC) [4, 5].

Phenotypic classification is proposed to describe the various forms of the disease. It is useful for the diagnosis and differential diagnosis of DILI and helps establish causality (since different phenotypes are associated with different drugs).

There is no generally accepted classification by phenotype. The most frequently identified phenotypes, their laboratory characteristics (type), and morphological expression are presented in Table 2. The most significant phenotypes are discussed below (Section 1.6 "Clinical picture of a disease or condition (group of diseases or conditions)").

1.5.5. Histological classification of DILI

Currently, there is no single validated histological classification of DILI.

Morphological changes in DILI are varied and can mimic virtually all liver diseases, with signs of acute and chronic damage, advanced fibrosis, or cirrhosis [2, 45]. Examination of a patient's liver biopsy allows to determine the nature of the histological damage, but is not necessary in most cases of DILI (see Section 2.4.1 "Pathological examination") [46, 47].

In the hepatocellular pattern of DILI, the following may be detected: necroinflammatory changes in liver biopsies (inflammatory infiltrates and necrosis of varying severity in the lobules (focal, confluent, bridging); portal and periportal inflammation; borderline hepatitis; signs of apoptosis; granulomas, etc., which often corresponds to the of acute or chronic hepatitis. Changes may be accompanied by signs of cholestasis [46].

In the cholestatic pattern of DILI, the following signs may be detected in biopsy samples:

- pure cholestasis — accumulation of bile in dilated tubules and inside the cytoplasm of hepatocytes without signs of concomitant inflammation;
- chronic cholestasis, which persists for a long time and leads to severe damage to the bile ducts and their loss [48]. If more than 50 % of the bile ducts are lost, VBDS is diagnosed;
- acute cholestatic hepatitis - the presence of cholestasis is accompanied by more pronounced lobular inflammation [49].

Drug-induced steatosis and steatohepatitis are less commonly diagnosed histological manifestations of DILI. DILI is classified into microvesicular, macrovesicular, and mixed steatosis [50].

DILI with vascular damage can lead to the development of nodular regenerative hyperplasia, obliterating portal venopathy and sinusoidal obstruction syndrome (veno-occlusive disease) [47, 51].

Also, histological signs specific to the causative drug have been described: frosted glassy cytoplasm of hepatocytes when taking phenytoin** and barbiturates [52]; phospholipidosis (hepatocytes with foamy cytoplasmic granularity) during treatment with antimalarial drugs [50, 53] and others.

Table 2. Main phenotypes of DILI, their comparison with pattern and morphological patterns

Phenotype	Laboratory pattern	Main morphological features
Acute liver necrosis	Hepatocellular	Centrilobular necrosis
Acute hepatitis	Hepatocellular	Acute hepatitis
Acute cholestatic hepatitis	Cholestatic and mixed	Cholestatic hepatitis
DRESS syndrome with liver involvement	Mostly cholestatic	Zonal or confluent necrosis, lymphocytic-eosinophilic infiltrate
Drug-induced autoimmune-like hepatitis	Hepatocellular	Signs of autoimmune hepatitis (lymphoplasmacytic periportal or lobular hepatitis)
Acute/pure cholestasis	Cholestatic	Intrahepatic cholestasis
Vanishing bile duct syndrome	Cholestatic	Ductopenia
Immune-mediated hepatitis	Hepatocellular	Panlobular hepatitis or centrozonal necrosis, lymphocytic-eosinophilic infiltrate
Secondary sclerosing cholangitis (drug-induced secondary sclerosing cholangitis)	Cholestatic and mixed	Cholangitis
Steatosis and steatohepatitis	Hepatocellular is possible	Micro- or macrovesicular steatosis, steatohepatitis
Sinusoidal obstruction syndrome/veno-occlusive liver disease	Hepatocellular	Damage to the sinusoidal endothelium, obstruction of the vascular lumen
Peliosis hepatitis	–	Formation of peliosis lacunae
Nodular regenerative hyperplasia	–	Benign proliferation of hepatocytes forming nodules
Benign and malignant tumors	–	Adenoma, carcinoma, cholangiocarcinoma, angiosarcoma

The presence of signs of fibrosis and/or liver cirrhosis in biopsies determines the long-term (chronic) course of liver disease [2, 54].

Certain morphological changes in the liver are associated with the prognosis of DILI [2]. Ductal involvement serves as a marker of a worse prognosis of DILI, whereas the presence of eosinophilic infiltration and granulomas in liver biopsies is associated with a better outcome of the disease [54, 55].

1.5.6. Classification of DILI by severity

An increase in the level of transaminases (ALT in particular) cannot be an independent basis for assessing the severity of DILI, since it does not serve as a prognostic marker for a particular outcome of the disease.

The International DILI Expert Working Group proposed a scale with four degrees of severity (Table 3) [56].

When assessing the hepatotoxicity of antitumor drugs, the severity of adverse reactions from the liver is assessed using the criteria of the US National Cancer Institute (Common Terminology Criteria for Adverse Events, CTCAE), which are specified in Appendix D2.

1.6. Clinical presentation of the disease or condition (group of diseases or conditions)

The clinical presentation of DILI depends on its laboratory type, clinical phenotype, as well as the severity of liver damage (whether there are signs of liver failure or not), and whether it is acute or chronic. In some cases, DILI is asymptomatic and is detected through laboratory tests or imaging (e.g., focal nodular hyperplasia of liver adenoma). In addition, some drugs have well-documented hepatotropic adverse reactions with specific clinical symptoms and characteristics.

Typical and non-specific clinical signs of hepatocellular liver damage are fatigue and weakness, sometimes a feeling of heaviness in the right hypochondrium, jaundice (with an increase in the level of bilirubin in the blood, usually due to both of its fractions).

With the cholestatic pattern of DILI, patients complain of itching of the skin (traces of scratching are visible on the body), which often disrupts their sleep; jaundice (the bilirubin level increases mainly due to the direct fraction).

The development/addition of liver failure is clinically manifested by hepatic encephalopathy (HE) of varying severity (latent and overt), hemorrhagic syndrome (ecchymosis, mainly at injection sites), sometimes edema and ascites due to impaired albumin synthesis, especially in the chronic course of DILI with advanced fibrosis/cirrhosis.

In mixed pattern of DILI, the above symptoms may be combined.

Some forms of DILI have specific symptoms that help establish a diagnosis.

Drug-induced autoimmune-like hepatitis

Drug-induced autoimmune-like hepatitis (DI-ALH, other definitions: autoimmune-like drug-induced hepatitis, immune-mediated autoimmune hepatitis) is a liver disease caused by taking medications and mimicking classical autoimmune hepatitis (AIH), it belongs to the category of idiosyncratic and mediated reactions.

The term DI-ALH was proposed by experts as a result of joint work by the Drug-Induced

Table 3. Severity of DILI (International DILI Expert Working Group (2011)) [56, 57]

Severity	Diagnostic criteria
Mild	ALT ≥ 5 ULN or ALP ≥ 2 ULN and total bilirubin < 2 ULN
Moderate	ALT ≥ 5 ULN or ALP ≥ 2 ULN and total bilirubin ≥ 2 ULN or presence of hepatitis symptoms*
Severe	ALT ≥ 5 ULN or ALP ≥ 2 ULN and total bilirubin ≥ 2 ULN or presence of hepatitis symptoms* and at least one of the following criteria is met: - INR > 1.5 - ascites and/or encephalopathy, disease duration < 26 weeks, no cirrhosis - acute failure of another organ due to DILI
Fatal/Transplantation	Death or liver transplantation due to DILI

Note: ** — symptoms of hepatitis include: fatigue, weakness, nausea, vomiting, pain in the right hypochondrium, itchy skin, rash, jaundice, loss of appetite, unmotivated, unintentional weight loss.*

Liver Injury Consortium and the International Autoimmune Hepatitis Group [58].

According to some studies, DI-ALH accounts for 2.0–9.2 % of registered cases of DILI [59–62].

The clinical presentation may include general symptoms such as weakness, fatigue, nausea, loss of appetite, fever, and joint pain. Liver manifestations may include jaundice, dark urine, light-colored stool, hepatomegaly, and pain or discomfort in the right upper quadrant.

More than 40 different drugs have been described to cause DI-ALH, including nitrofurantoin, methyldopa**, minocycline, interferons, HMG-CoA reductase inhibitors (mainly atorvastatin**, less often simvastatin** and rosuvastatin, which accounts for 8.5–27.2 % of all DILI associated with the use of HMG-CoA reductase inhibitors (statins) [63], methylprednisolone**, diclofenac**, antitumor drugs of the protein kinase inhibitor class (most often imatinib**, less often pazopanib**) and monoclonal antibodies and antibody conjugates (e.g., ipilimumab**, nivolumab**, etc.), immunosuppressants from the group of tumor necrosis factor alpha (TNF-α) inhibitors (e.g., infliximab**, adalimumab**), herbal products and dietary supplements (for example, Tinospora cordifolia). However, some medications and vaccines can trigger the development of true AIH [58, 64–66].

Laboratory and histological signs that can be detected in DI-ALH are identical to those in AIH, and specific markers that would allow differentiation between these two conditions are absent. DI-ALH is characterized by the hepatocellular pattern of DILI, an increase in the level of serum immunoglobulin G (IgG), and the detection of autoantibodies. Histological changes determined in the liver in DI-ALH are also close to those in classical AIH, with the exception of the absence of pronounced fibrosis and cirrhosis [67]. At the same time, with long-term use of drugs that cause DI-ALH, cases of cirrhosis have also been recorded [68].

The main difference between DI-ALH and true AIH is the absence of relapses [58, 68] after discontinuation of immunosuppressants.

In recent years, there have been significant changes in the spectrum of drugs that cause DI-ALH, which is associated with an increase in the use of biological drugs, the widespread introduction of immunotherapy in oncology, and changes in approach to the treatment of various diseases.

DRESS-syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)

A rare form of DILI is DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), with an incidence of 0.9 per 100,000 persons and 2.18 to 40 per 100,000 hospitalized patients [69]. According to the prospective RegiSCAR study, the mortality rate is 1.7 % [70].

The most common medications, that lead to the development of DRESS syndrome are antiepileptic drugs (carbamazepine**, lamotrigine, phenobarbital**, phenytoin**, oxcarbazepine**), systemic antibacterial drugs (amoxicillin**, ampicillin**, azithromycin**, levofloxacin**, minocycline, co-trimoxazole [sulfamethoxazole + trimethoprim]**, vancomycin**), antituberculosis drugs (ethambutol**, isoniazid**, pyrazinamide**, rifampicin**), NSAIDs (acetylsalicylic acid**, celecoxib, diclofenac**, ibuprofen**, piroxicam), as well as drugs such as allopurinol**, amitriptyline**, dapsone**, hydroxychloroquine**, imatinib**, nevirapine**, omeprazole**, sulfasalazine** [69]. Three key components are considered in the pathogenesis of DRESS syndrome: genetic predisposition; altered drug metabolism, particularly of antiepileptic drugs with aromatic ring structures; and reactivation of human herpes virus type 6, which leads to a T-lymphocyte-mediated inflammatory response and tissue damage.

When collecting anamnesis, it is important to remember that clinical manifestations of DRESS syndrome are usually determined 2–6 weeks after the administering of the drug that triggers the pathological process [69, 71].

DRESS syndrome clinically manifests as a rash (in some cases, urticaria) with eosinophilia in blood tests and systemic symptoms, both general (chills, fever, lymphadenopathy) and those associated with the involvement of internal organs, particularly the liver. A close examination of the skin reveals a maculopapular rash, and in some cases, vesicles, bullae, pustules, purpura, facial edema, cheilitis, and erythroderma.

Liver involvement can manifest in various ways: from asymptomatic elevations in serum transaminases and alkaline phosphatase (ALP) by more than 2 and 1.5 times the ULN, respectively, to extensive liver necrosis with an increase in ALT levels by more than 10 times and clinical signs of liver failure with coagulopathy, HE, and jaundice. Damage to other internal organs is also observed, with the development of pneumonitis, myocarditis, pericarditis, nephritis, and colitis. Damage to internal organs, including the liver, is the primary cause of mortality in this syndrome [70].

Characteristic hematological changes include leukocytosis, eosinophilia (90 %), and/or

mononucleosis (40 %). It is important to note that elevated liver enzymes may persist for many months after clinical resolution of DRESS syndrome [69, 72, 73].

DRESS syndrome can serve as an inducer for the development of autoimmune diseases (autoimmune hemolytic anemia, Graves' disease, etc.), while DI-ALH as an outcome of this condition has not been described in the literature [69, 73, 74].

Liver injury associated with immune checkpoint inhibitors (ICIs): immune-mediated hepatitis and secondary sclerosing cholangitis (DI-SSC)

Immune-mediated hepatitis refers to the category of immune-mediated adverse reactions during treatment with ICIs such as ipilimumab**, nivolumab** and pembrolizumab**. In the overwhelming majority of cases, it develops due to using a combination of ipilimumab** and nivolumab** (13–83 %) [75, 76], with monotherapy with ipilimumab** its frequency is 4.5 %, with monotherapy with anti-PD-1 inhibitors — 1.8 % [75].

The median time to clinical presentation of immune-mediated hepatitis was 47 days (range 4–476), and the median time to peak ALT elevation was 71 days (range 4–478) [76].

Immune-mediated hepatitis presents with nonspecific symptoms: weakness, in some cases, fever, a feeling of heaviness and pain in the right upper quadrant, and jaundice. If patients develop liver failure, HE and coagulopathy occur. Laboratory abnormalities in the vast majority of cases are consistent with the hepatocellular pattern of DILI, with elevated serum transaminases of CTCAE' Grade 3 or higher. Cases of mixed DILI occur. Immune-mediated hepatitis is a diagnosis of exclusion.

Programmed cell death inhibitors type 1 (anti-PD-1) are used to treat many malignancies. Among their immune-mediated adverse reactions, DI-SSC has been described, occurring with a frequency of 0–4.5 % and characterized by cholestatic hepatotoxicity. The main drugs that cause this type of hepatotoxicity are nivolumab**, pembrolizumab**, avelumab**, durvalumab**, and atezolizumab** [77].

DI-SSC presents with the following clinical symptoms: general weakness, fever, skin lesions, back pain, loss of appetite and vomiting, diarrhea, abdominal pain or discomfort, and jaundice. Laboratory tests reveal elevated levels of bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT), serum transaminases, and IgG. Visual and endoscopic diagnostic methods reveal the following abnormalities: stenosis of the intra- and extrahepatic bile ducts, including multiple strictures; dilation and predominantly diffuse thickening of the bile duct wall. Histological examination of liver biopsies in most cases reveals inflammatory changes with infiltration of $CD8^+$ T cells.

Features of DI-SSC associated with the use of ICI (in particular, anti-PD-1): manifestation on average 55 days after the start of antitumor treatment, biliary dilation and thickening of the bile duct wall without obstruction and/or multiple strictures of the intrahepatic bile ducts, liver dysfunction with a dominant increase in the activity of enzymes reflecting cholestasis (ALP Grade 2 and higher according to the criteria of CTCAE v 5.0 (2017)), increased GGT levels (see Appendix D2), normal serum IgG4 levels and moderate or weak response to steroid therapy.

Diagnostic criteria for this condition have not been developed; however, in individuals receiving ICI treatment, with the development of cholestasis with an increase in alkaline phosphatase activity of Grade 2 or higher according to CTCAE criteria, it is advisable to use methods of visualization of the biliary tree for diagnostic purposes [75, 77].

In addition to ICI, the development of DI-SSC can be caused by taking ketamine**, docetaxel**, moxifloxacin**, amoxicillin + clavulanic acid**, cefazolin**, etc. [78–80].

Vanishing bile duct syndrome (VBDS)

VBDS is a rare form of cholestatic DILI characterized histologically by the loss of at least half of the interlobular bile ducts or a bile duct to portal tract ratio of < 0.5. This condition typically develops 1–6 months after an episode of severe cholestatic hepatitis, often with immunoallergic features, which does not resolve.

Progressive destruction of the intrahepatic bile ducts with the development of ductopenia is usually independent of the dose of a drug or herbal product. Immune-mediated or direct damage to cholangiocytes by drugs or their metabolites entering the bile, and prolonged exposure to toxic bile salts with impaired protective functions of the biliary epithelium are the main mechanisms of cholangiocyte damage.

Clinical presentation: fatigue, persistent itching, jaundice, xanthomas and xanthelasmas.

Immunoallergic signs include rash, fever, facial swelling, lymphadenopathy, and eosinophilia; in more severe cases, Stevens-Johnson syndrome or toxic epidermal necrolysis. The disease may lead to liver failure and require transplantation. In some cases, recovery or clinical improvement is observed in the patient; however, histological

examination of the liver biopsy continues to reveal ductopenia and fibrosis of varying degrees. Laboratory parameters show persistently elevated levels of ALP and bilirubin, as well as bile acids (BA) and cholesterol. The development of VBDS is associated with the use of beta-lactam antibacterials, penicillins (e.g., amoxicillin + clavulanic acid** and others), macrolides, fluoroquinolones, sulfonamides, systemic antifungals, NSAIDs, phenothiazine derivatives, tricyclic antidepressants, aromatic antiepileptic drugs, etc.

The differential diagnosis includes sclerosing cholangitis, primary biliary cholangitis, Hodgkin's disease, and others. VBDS is a histological diagnosis, but it can be suspected based on the above-mentioned clinical signs and laboratory data [81–83].

Sinusoidal obstruction syndrome (hepatic veno-occlusive disease)

Sinusoidal obstruction syndrome (hepatic veno-occlusive disease) is a rare form of liver injury that occurs after cytoreductive therapy prior to hematopoietic stem cell transplantation, exposure to certain anticancer medications (oxaliplatin**, gemtuzumab ozogamicin, ICI, etc.), and pyrrolizidine alkaloids. The incidence of sinusoidal obstruction syndrome ranges from 8.3 to 54 % in patients receiving oxyplatin-based anticancer regimens, such as FOLFOX and FOLFIRI for the treatment of colorectal cancer.

Diagnosis of this condition is challenging, as clinical criteria have low specificity, and reliable noninvasive biomarkers are lacking. Sinusoidal obstruction syndrome is thought to be caused by damage to sinusoidal endothelial cells, leading to dilation and capillarization of the sinusoids, fibrosis, and obstruction of the central veins, with or without nodular regenerative hyperplasia.

This condition should be considered if a patient experiences elevated aspartate aminotransferase (AST) levels combined with thrombocytopenia while taking certain medications. The complete clinical presentation includes enlarged liver and spleen and jaundice [84].

Enlarged spleen correlates with increased severity of sinusoidal liver injury and may serve as a simple method to identify patients at risk for developing this form of toxicity.

Oxaliplatin**-induced spleen enlargement should be considered as a potential cause of persistent thrombocytopenia after oxaliplatin treatment** [85].

In rare cases, sinusoidal obstruction syndrome associated with oxaliplatin**-based antitumor regimens can lead to portal hypertension (PH) with the development of esophageal and gastric varices, a risk of bleeding, massive ascites, and pancytopenia. Such patients may require surgical and endoscopic treatment [86].

Drug-induced acute liver failure (DI-ALF)

DI-ALF is a condition in which the loss of hepatocyte function occurs over several days or weeks and is accompanied by the development of hepatic embolism and coagulopathy under the influence of medications, dietary supplements, or herbal products. Patients with this condition have no history of chronic liver disease.

According to international literature data, approximately 39–60 % of DI-ALF is associated with paracetamol overdose**, 46 % with the use of systemic antimicrobials and other medications and dietary supplements [87].

The time of onset of DI-ALF and the characteristics of its clinical course depend on the causative drug. For example, with paracetamol** overdose, symptoms manifest within a few hours; with isoniazid** use, a subacute DI-ALF is observed, and PE usually occurs at least 2–4 weeks after the onset of the disease.

DI-ALF always involves hepatocellular liver injury with elevated serum transaminase and bilirubin levels. Laboratory signs of impaired liver synthetic function include hypocoagulation. DI-ALF due to paracetamol** overdose is characterized by very high serum transaminase levels, often reaching > 10,000 IU/L, combined with a moderate increase in bilirubin (< 5 mg/dL).

Signs of DI-ALF:

General symptoms: fatigue, nausea, loss of appetite, discomfort in the right hypochondrium.

As liver failure progresses, jaundice, darkening of urine, varying degrees of severity of PE up to coma and cerebral edema, hypocoagulation with hemorrhagic syndrome occur.

Specific therapy is used for DI-ALF due to paracetamol overdose** (see Section 3). Severe cases of DI-ALF may require LT (see Section 3.3 "Surgical treatment") [87, 88].

2. Diagnosis of a disease or condition (group of diseases or conditions), medical indications and contraindications for the use of diagnostic methods

Diagnosis of DILI includes assessment of the following:

- interval between initiation of drug administration and development of liver damage;
- clinical symptoms;
- duration and course of the recovery period;

• risk factors;
• exclusion of other causes of liver damage;
• consideration of previous data on drug hepatotoxicity and establishment of causality (see Section 2.5.1);

Additional factors that may be considered in a diagnosing include:

– response to rechallenge with the drug (if administered) (see Section 2.5.1);

– pathological examination data from liver tissue (if a liver biopsy was performed) (see Section 2.4.2) [14, 89].

Identifying causative drug (or dietary supplement, or herbal product) is a key point in the diagnosis of DILI and the basis for deciding whether to discontinue the drug (discussed in detail in Section 2.5).

• It is recommended that patients with suspected DILI undergo an appointment (examination, consultation) with a general practitioner or a family doctor or a gastroenterologist to establish a diagnosis, prescribe examination and treatment. [14, 90].

Grade of recommendations – C;
level of evidence – 5.

Comments. DILI should be suspected in any of the following circumstances:

1) if the activity of initially normal values of serum ALT, AST, ALP and total bilirubin (TBL) increases after the start of drug administering;

2) when the values of serum ALT, AST, ALP and bilirubin increase two or more times from the initial values or when liver function worsens after the start of taking the drug in patients with previously altered liver panel laboratory tests, when this cannot be explained by the course of a pre-existing chronic liver disease;

3) in patients with symptoms of liver disease that arose after starting the drug;

4) in patients with an unknown cause of liver damage or disease, with other possible etiologic factors excluded during the examination process [45].

Criteria for establishing the diagnosis/condition: the criteria listed in Table 4 are used to diagnose DILI.

• For patients receiving drugs and/or dietary supplements and/or herbal products, it is recommended to use the criteria specified in the Table 4 to diagnose suspected DILI [4, 56].

Grade of recommendation – C;
level of evidence – 5.

Comments. In 2011, the International Expert Working Group increased the threshold values for liver panel parameters compared to those proposed previously in order to avoid overdiagnosis of DILI and unjustified drug discontinuation [4]. A transient increase in serum transaminase activity may be due to the adaptive response of the liver to the effects of various agents. An example of such adaptation (the phenomenon of tolerance) is the initial increase in ALT activity in response to taking HMG-CoA reductase inhibitors (statins) [91]. An isolated increase in GGT or bilirubin levels is not a sign of DILI [92]. Certain phenotypes of DILI, such as steatosis or focal liver changes, may not be accompanied by laboratory abnormalities and are diagnosed using other examination methods [56].

• **It is recommended** to use lower laboratory criteria for DILI in patients with underlying severe liver diseases and risk factors for severe DILI: a) increased ALT activity in the blood > 2 ULN, or b) increased levels of bound (conjugated) bilirubin > 2 ULN, or c) increased activity of AST, alkaline phosphatase in the blood and TBL level in the blood (one of the indicators > 2 ULN) [4, 45, 93].

Grade of recommendation – C;
level of evidence – 5.

Comments. In patients with pre-existing severe liver disease, mortality or the need for LT when DILI develops is 3–4 times higher compared to the general population [94, 95]. In this category of patients, DILI may manifest itself as a deterioration in parameters that reflect liver function: an increase in the level of bilirubin and its fractions and/or an increase in the international normalized ratio (INR) [4].

• **It is recommended** that in patients with underlying liver disease and initially altered laboratory parameters (before using a drug, dietary supplement, or herbal product suspected of causing DILI), their average baseline values be used instead of the ULN in order to avoid overdiagnosis of DILI [56].

Grade of recommendation – C;
level of evidence – 5.

Comments. If DILI is suspected, the following factors should be taken into account: pre-existing liver disease or the possibility of an initial asymptomatic increase in serum transaminase activity in some patients [96]. The fold increase in the mean values of baseline altered laboratory parameters of liver function is shown in Table 4 [56].

• **It is recommended** that all patients with suspected DILI undergo differential diagnostics with other causes of deterioration in laboratory parameters of the liver and/or the appearance of clinical symptoms/worsening of the clinical course of liver disease [93].

Grade of recommendation – C;
level of evidence – 5.

Table 4. Diagnostic criteria for drug-induced liver injury (based on the recommendations of the International Expert Working Group (2011) and the CIOMS criteria (1999) with amendments) [4, 45, 56]

A causal relationship between the use of a drug (or dietary supplement, or herbal product) in combination with one or more of the following signs of liver injury*:
a) increased ALT activity ≥ 5 ULN*, **
b) increased alkaline phosphatase activity ≥ 2 ULN (in the absence of known bone disease)*, ***
c) increased ALT activity ≥ 3 ULN and increased total bilirubin level > 2 ULN*
d) elevated laboratory values that do not reach the level of (a), (b), (c) in the presence of clinically significant symptoms
e) convincing evidence of liver damage (e.g., histological findings, imaging studies) in the absence of (a), (b), (c)
f) increased ALT activity ≥ 2 ULN* in patients at risk of severe DILI (e.g., previous liver disease with severe liver damage)

Note: ** — if elevated laboratory values were observed prior to treatment with a suspected drug (previous liver injury), the ULN is replaced by the mean baseline values prior to exposure; ** — the use of AST instead of ALT is possible in cases where AST predominates over ALT and there is no known muscle damage; *** — hepatic origin of ALP can be confirmed by an increase in GGT activity.*

2.1. Complaints and anamnesis

The collection of complaints and anamnesis should be aimed at identifying the likely agent (medicines, dietary supplements, and other herbal products) that led to the development of DILI, as well as possible underlying and triggering factors. A detailed clarification of the course of such a case is necessary: the duration and dosage of the medication, the start and end dates of its use, and the history of previous use of this medication. It is necessary to exclude the possible role of other factors: heredity, epidemiological history, allergic history, the presence of previous adverse reactions/tolerance to drugs, previous medical procedures (blood transfusion, etc.), consumption of alcohol or other potentially harmful substances (frequency, duration, dose). The presence and course of other liver diseases, comorbidities, and underlying conditions (chronic and acute diseases, pregnancy) should be clarified. There is insufficient evidence to support the assertion that age, gender, race, and ethnicity are reliable predictors of the risk of drug-induced hepatotoxicity.

Clinical manifestations of DILI vary from an asymptomatic variant of the disease to severe fulminant forms with ALF, and also depend on the pattern of DILI (cholestatic, hepatocellular, mixed). These may include fatigue and weakness, altered consciousness, increased body temperature; loss of appetite; weight loss, nausea, vomiting, abdominal pain; itching, skin rash; jaundice (changes in the color of the skin and mucous membranes, feces, urine); bleeding [2, 14, 33, 97]. In some cases, medical history data forms the basis of differential diagnosis. For example, patients with a recent history of hypotension, sepsis, or heart failure are at risk for ischemic liver injury, which is typically characterized by a rapid and marked increase in serum transaminase activity followed by a rapid decrease with normal or borderline bilirubin levels. This clinical presentation may mimic DILI.

In patients with a predominance of AST activity over ALT and high GGT levels, the possibility of alcoholic hepatitis should be considered, especially in combination with other clinical and laboratory markers of this disease [98, 99].

Patients with DILI, altered consciousness, and coagulopathy (INR > 1.5) are highly likely to have ALF. Their indications and contraindications for LT should be assessed, as the probability of spontaneous recovery is less than 30 % [20, 100] (see Section 3.3 “Surgical treatment”).

2.2. Physical examination

Physical examination of patients with DILI is carried out according to a standard protocol and includes an assessment of the general condition of a patient, their consciousness, presence of fever, changes in the skin, mucous membranes and subcutaneous tissue (rashes, jaundice, dryness, excoriations, petechiae, ecchymoses, hematomas, edema and ascites), determination of the size and elasticity of the liver (hepatomegaly of varying degrees of severity, liver compaction) and spleen (splenomegaly is not characteristic of DILI, with the exception

of cases of chronic liver damage with the development of PH). With asymptomatic DILI, visible clinical signs may be completely absent. [14].

Physical examination may also suggest liver damage associated with drug hypersensitivity syndrome (DRESS) [101], which includes skin rash, lymphadenopathy, and fever (see Section 1.6).

2.3. Laboratory diagnostic tests

Diagnostic tests performed when DILI is suspected can be divided into three groups:

a) tests aimed at assessing the type and severity of liver damage;

b) first-line differential diagnostic tests aimed at excluding the most common liver diseases that can mimic DILI;

c) second-line differential diagnostic tests aimed at excluding rarer liver diseases that can mimic DILI.

Group (a) tests are performed on all patients with suspected DILI.

First-line differential diagnostic tests are performed for all patients with the corresponding pattern of DILI. Second-line differential diagnostic tests are performed only if the first-line tests are negative (hereinafter, these are referred to as those performed in selected patients).

2.3.1. Basic laboratory diagnostic tests

Tests aimed at assessing the pattern and severity of liver damage

Laboratory parameters of liver function in most DILI phenotypes serve as the leading method for diagnosing DILI, determining its type, and assessing the effect of treatment.

• **It is recommended** to perform a complete blood count (CBC) test for patients with suspected and established DILI to identify signs of drug hypersensitivity and differential diagnosis [2, 71, 92].

Grade of recommendation — C;
level of evidence — 5.

Comments. In the haemogram, attention should be paid to platelet levels (reflect the stage of liver disease), hemoglobin, and red blood cell counts (necessary to differentiate from suprahepatic jaundice in indirect hyperbilirubinemia). DRESS syndrome is characterized by leukocytosis, often with atypical lymphocytes, and eosinophilia [71, 102–104].

• **It is recommended** to perform a blood chemistry test with determination of the activity of ALT, AST, ALP, GGT, level of total, direct (conjugated) and indirect (unconjugated) bilirubin, the level of albumin, the international normalized ratio (INR) and prothrombin (thromboplastin) time for patients with a suspected and established diagnosis of DILI for the diagnosis of DILI, identification of its pattern (cholestatic, hepatocellular or mixed) and assessment of severity [2, 43, 105].

Grade of recommendation — C;
level of evidence — 5.

Comments. A moderate increase in serum transaminases during the first weeks of therapy with some drugs (e.g., HMG-CoA reductase inhibitors) most often reflects an adaptive response. In the cholestatic pattern of DILI, an increase in serum ALP activity is accompanied by an increase in GGT levels [56]. ALT activity is used to detect and monitor the hepatocellular pattern of DILI [106, 107]. New serum biomarkers are being developed (glutamate dehydrogenase, cytokeratin 18, etc.) [108]. Jaundice suggests a significant loss of functioning hepatocytes [109], and the hepatocellular pattern of DILI with jaundice is characterized by the most severe outcomes [11]. Bilirubin and INR levels are used to determine the severity of DILI. An increase in INR/prothrombin time may be a manifestation of ARF. Albumin and hemostasis parameters reflect liver function.

• **It is recommended** that in patients with a suspected and established diagnosis of DILI and elevated laboratory parameters of the liver condition, the R coefficient (the ratio of the fold increase in the activity of ALT and ALP to the ULN) be determined at the onset of the disease to determine the pattern of DILI (hepatocellular, cholestatic or mixed) and to select the examination and treatment approach [2, 43].

Grade of recommendation — C;
level of evidence — 5.

Comments. A value of $R \geq 5$ identifies the hepatocellular type of liver damage (predominantly increased ALT and AST), a value of $R < 2$ identifies the cholestatic type of liver damage (predominantly increased ALP), a value of $5 > R > 2$ reflects a mixed pattern of DILI [4]. The pattern of DILI (R coefficient) allows to develop approach to differential diagnosis and treatment of DILI and is taken into account when assessing the causative interrelations between drugs and liver damage (causality) (see Section 2.5.1) [110–112].

• In all patients with suspected hepatocellular DILI, **it is recommended** to rule out AIH and to detect DI-ALH evaluating the serum IgG level, and autoantibodies: ANA, anti-smooth muscle antibodies (ASMA) using indirect immunofluorescence [2, 43, 60, 61, 113, 114].

Grade of recommendation — C;
level of evidence — 5.

Comments: Some drugs can cause DI-ALH (HMG-CoA reductase inhibitors, antitumor drugs

of the protein kinase inhibitor class, immunosuppressants from the TNF-α inhibitor group); its laboratory signs are identical to those of AIH, and specific differential diagnostic markers are absent. DI-ALH is characterized by the hepatocellular pattern of DILI, an increase in the level of serum IgG, and the detection of autoantibodies [67]. Low levels (e.g., titer is less than 1 : 80) of serum autoantibodies are not informative [115].

• **It is recommended** to determine antimitochondrial antibodies (AMA) and antinuclear antibodies (ANA) in serum by indirect immunofluorescence (IFA) with assessment of the staining patterns in all patients with suspected and established cholestatic and mixed DILI to exclude primary biliary cholangitis [2, 43, 116].

Grade of recommendation — C;
level of evidence — 5.

Comments. Anti-mitochondrial antibodies (AMA, subtype AMA-M2), directed against enzymes of the pyruvate dehydrogenase complex, have high diagnostic specificity in primary biliary cholangitis (PBC) [117]. In the presence of PBC-specific antibodies (AMA, anti-gp 210 and anti-sp 100), ANA patterns AC-21, -12 and -6 (in accordance with International Consensus on Antinuclear Antibody (ANA) Patterns (ICAP)) are detected in IFA [118].

2.3.2. Differential laboratory diagnostics for DILI

Calculating the R coefficient allows for targeted differentiation of DILI from other causes of liver injury, including hepatocellular, cholestatic, or mixed patterns. The differential diagnosis of acute hepatocellular injury includes acute (primarily viral) hepatitis, alcoholic liver disease, AIH, ischemic liver injury, Budd — Chiari syndrome, and Wilson's disease. Extrahepatic causes of elevated values must be excluded.

In the case of a cholestatic pattern of DILI, diagnostic evaluation should be aimed at excluding causes of extrahepatic cholestasis (diseases of the pancreatobiliary tract — cholelithiasis, tumors, strictures, etc.) and primary cholestatic diseases (such as primary biliary cholangitis). It should be kept in mind that acute biliary obstruction may initially have a hepatocellular nature of damage but subsequently demonstrate a cholestatic pattern.

In the differential diagnosis, it is necessary to first exclude the most common causes of liver damage (for example, in the hepatocellular type — viral hepatitis, etc.), and only then, in individual patients, rarer diseases (for example, Wilson's disease, hereditary hemochromatosis).

First-line differential diagnostic tests aimed at excluding the most common liver diseases that can mimic DILI

In patients with suspected DILI and a predominant increase in AST over ALT, **it is recommended** to determine the total creatine kinase (a general clinical biochemistry blood test) to exclude the muscular genesis of hyperenzymemia [2].

Grade of recommendation — C;
level of evidence — 5.

• In patients with suspected hepatocellular or mixed DILI to exclude acute viral hepatitis A, B, C, **it is recommended** to detect serum antibodies to the hepatitis A virus IgM (anti-HAV IgM), the surface antigen of the hepatitis B virus (HBsAg), antibodies to the hepatitis C virus (anti-HCV), and in some patients — to determine ribonucleic acid (RNA) of hepatitis C (polymerase chain reaction (PCR), qualitative study) in the blood [2, 43].

Grade of recommendation — C;
level of evidence — 5.

Comments. Acute viral hepatitis can mimic DILI, most often of the hepatocellular pattern [119, 120]. In a recent report from the prospective DILIN study, acute hepatitis C virus infection was mimicking DILI in 1.5 % of cases, leading to the recommendation to exclude acute hepatitis C infection in patients with suspected acute hepatocellular DILI by detecting HCV RNA in the blood [94, 119].

Second-line differential diagnostic tests aimed at excluding rarer liver diseases that can mimic DILI

• To exclude acute hepatitis E in patients with suspected DILI, **it is recommended** to consider detection of anti-HEV IgM and anti-HEV IgG antibodies in serum, as well as hepatitis E virus RNA in feces using the PCR method, if it is available for differential diagnosis [2, 43].

Grade of recommendation — C;
level of evidence — 5.

Comments. Acute hepatitis E virus infection, which is increasingly being reported in developed countries, may mimic DILI. Testing for acute hepatitis E should be considered in selected cases: no obvious cause for liver injury; DILI pattern and phenotype atypical for the suspected DILI; sharp elevation of transaminases in individuals living in or visiting endemic areas, as well as in the elderly. [121, 122].

• **It is recommended** to test the level of serum ceruloplasmin and daily excretion of copper in the urine in patients with suspected DILI for the differential diagnosis between hepatocellular or mixed DILI and disorder of copper metabolism (Wilson's disease) [123].

Grade of recommendation — C;
level of evidence — 5.

• **It is recommended** that patients with suspected DILI consider testing for transferrin saturation and blood ferritin levels to differentiate DILI with a hepatocellular or mixed pattern from primary hemochromatosis [2, 43, 57, 113].

Grade of recommendation — C;
level of evidence — 5.

Comments. A decrease in serum ceruloplasmin levels is the basis for further testing to exclude Wilson's disease: testing of copper levels in the blood and urine, slit-lamp examination of the eyes for the presence of Kayser — Fleischer rings, genetic testing of the ATP7B gene [123]. Transferrin saturation and ferritin levels are the main screening tests for hemochromatosis [124].

• **It is recommended** to test patients with suspected DILI for antibodies to Herpes simplex virus types 1 and 2 IgM and IgG, antibodies to Varicella zoster virus IgM and IgG, antibodies to cytomegalovirus IgM and IgG — IgM VCA, IgG EA, IgG VCA, antibodies IgG to Epstein — Barr virus for the differential diagnosis of DILI of the hepatocellular or mixed pattern with herpes infections [2, 43].

Grade of recommendation — C;
level of evidence — 5.

• **It is recommended** that patients with suspected hepatocellular DILI undergo screening for thyroid diseases and celiac disease for their timely detection in order to avoid overdiagnosis of DILI [2].

Grade of recommendation — C;
level of evidence — 5.

Comments. Hypo- and hyperthyroidism, as well as celiac disease, can cause elevated transaminase activity and mimic DILI [2]. Screening for these diseases is carried out in accordance with existing clinical guidelines.

• **It is recommended** to consider checking serum ammonia level in patients receiving drugs, for diagnosis and differential diagnosis with other conditions, when clinical manifestations of hyperammonemia appear, if the method is available [125–128].

Grade of recommendation — C;
level of evidence — 3.

Comments. More than 70 drugs have been described implicated in hyperammonemia as a consequence of DILI or a disruption of metabolic processes due to the effects of drugs: valproate-induced hyperammonemia [125, 129], antitumor, antiepileptic drugs, psycholeptics, immunosuppressants, etc. [126]. Clinical signs of hyperammonemia are nonspecific: from loss of appetite and vomiting to altered mental state, seizures and coma [126, 127, 130]. Acute severe hyperammonemia can lead to fatal HE, and chronic hyperammonemia causes progressive cognitive, behavioral and other neuropsychiatric changes [126]. Serum ammonia levels usually correlate with the severity of clinical manifestations [130]. Some factors (hemolysis, delayed sample separation, or improper storage) may lead to artificially elevated serum ammonia levels [131]. There are no specific tests to confirm or exclude drug-induced hyperammonemia [127]. Testing serum for liver tests, urea levels, glucose, lactate, ketones, and acid-base balance are helpful in the differential diagnosis of hyperammonemia [132].

2.4. Instrumental examination

Visualization techniques for examining the abdominal organs in cases of suspected DILI are aimed at differential diagnosis with other diseases, primarily with mechanical jaundice and infiltrative processes in the cholestatic pattern of DILI.

• **It is recommended** that all patients with suspected DILI undergo a comprehensive ultrasound examination (US) of the abdominal organs for differential diagnosis with other diseases of the liver, biliary tract and other abdominal organs [2, 43].

Grade of recommendation — C;
level of evidence — 5.

Comments. US of abdominal organs is an accessible screening technique that allows for a primary assessment, differential diagnosis of DILI with other diseases of the liver and bile ducts (cholelithiasis, tumors, duct strictures, etc.), and also to exclude complications (PH, etc.) [133].

• **It is recommended** that all patients with suspected cholestatic and mixed pattern DILI undergo magnetic resonance cholangiopancreatography (MRCP) to exclude biliary tract involvement [2, 45, 79, 133].

Grade of recommendation — C;
level of evidence — 4.

Comments. MRCP is a reliable and safe technique for visualizing the biliary tree, which allows for the detection of DI-SSC and the differentiation of cholestatic and mixed types of DILI from other biliary tract diseases [2, 13, 45]. DI-SSC has been described with intra-arterial administering of pyrimidine analogues (fluoropyrimidines) [134], as well as after taking moxifloxacin**, atorvastatin** and dietary supplements [133]. The use of endoscopic retrograde cholangiopancreatography is limited to cases where other imaging techniques do not allow establishing a diagnosis and the expected benefit of the study outweighs the risks of adverse events [13].

• **It is recommended** that patients with suspected cholestatic DILI undergo endosonography of the pancreatobiliary zone (endoscopic ultrasound sonography, EUS) for differential diagnosis with other diseases when MRCP is insufficiently informative [2, 45].

Grade of recommendation — C; level of evidence —5.

Comments. EUS allows for very high-resolution imaging due to the proximity of the endoscope probe to internal structures and exceeds the resolution of MRCP [135]. EUS is indicated in cases of suspected cholestatic DILI, when MRCP is insufficiently informative and further differential diagnosis with diseases of the pancreatobiliary zone is necessary.

• In patients with suspected hepatocellular DILI, **it is recommended** to consider performing Doppler ultrasonography of the abdominal vessels to detect liver vascular damage and signs of portal hypertension [2, 45, 136].

Grade of recommendation — C; level of evidence — 5.

Comments. Some drugs can cause liver vascular damage. For example, systemic hormonal contraceptives can cause extrahepatic portal vein obstruction and intimal hyperplasia of the hepatic artery. Necrotizing vasculitis of the hepatic artery has been described following methamphetamine use (a toxicant) [137]. In some cases, DILI must be differentiated from liver vascular diseases of a different nature. The gold standard for diagnosing vascular thrombosis is angiography, but it is an invasive procedure [138]. Doppler ultrasonography is available, safe, and noninvasive; it is a first-line tool for diagnosing vascular occlusion, is relevant in diagnosing PH, and is indicated for differentiating DILI from Budd — Chiari syndrome and other vascular diseases [138]. Computed tomography scan (CT) of the abdominal cavity with intravenous contrast allows for more accurate visualization of the vessels.

• When there is a suspicion of liver vascular damage or a neoplasm of the hepatobiliary system in patients with suspected DILI, **it is recommended** to consider performing CT of abdominal organs with intravenous bolus contrast for differential diagnosis [2, 45].

Grade of recommendation — C; level of evidence — 5.

Non-invasive methods for assessing fibrosis (laboratory calculation methods, transient elastography) can probably be used in chronic DILI, but their data is indicative, since these tools have not been validated for use in DILI [14, 45]. The largest amount of information on the use of non-invasive methods has been published on a cohort studies of rheumatological patients taking methotrexate** for a long time [139, 140]. In these patients, liver transient elastography showed high sensitivity and specificity for ruling out advanced fibrosis [141, 142]. In addition, transient elastography is relevant in the management of patients with veno-occlusive disease in bone marrow transplantation [143].

2.4.1. Pathological examination

• **It is recommended** to consider performing a liver biopsy (US-guided percutaneous liver biopsy or laparoscopic liver biopsy) with pathological examination of a biopsy (surgical) liver specimen in patients with suspected or established DILI for diagnosis and/or differential diagnosis, if the biopsy results may affect the management approach and/or prognosis of the patient, and non-invasive methods have not provided sufficient information [2, 13, 45, 144].

Grade of recommendation — C; level of evidence — 4.

Comments. Histological evaluation of liver tissue is usually used to disprove alternative etiologies of the lesion, less often to confirm the diagnosis of DILI or to determine its phenotype [144–146]. Situations requiring it include: a) an increase in laboratory parameters of the liver or deterioration of liver function after discontinuation of the suspected drug; b) the absence of positive dynamics of laboratory parameters after discontinuation of the suspected drug (in the hepatocellular pattern, a decrease in ALT activity < 50 % within 30–60 days, in the cholestatic pattern, a decrease in ALP activity < 50 % within 180 days, the specified periods are approximate and can be changed in accordance with the clinical situation); c) suspicion of chronic DILI; d) suspicion of the onset of DILI in patients with pre-existing liver disease; e) differential diagnosis between DILI and conditions requiring a liver biopsy before prescribing treatment: DI-ALH and true AIH; suspicion of the onset of DILI in patients with pre-existing liver disease after organ transplantation to differentiate from graft-versus-host disease [2, 13, 45, 109, 111, 146].

2.5.1. Assessment of causality in suspected DILI

Identifying the causative interrelations of drugs, dietary supplements, and herbal products with DILI is a key point in the diagnosis of the disease, and the basis for deciding whether to discontinue the drug.

To prove causality, it is necessary to:

— determine the temporal sequence of drug exposure or withdrawal and changes in liver function tests;

– identify whether the clinical and diagnostic signatures of liver injury (phenotype) correspond to published data on the hepatotoxicity of the suspected medication;

– assess the dynamics of the condition after discontinuation of the suspected drug or dose reduction;

– evaluate the response to re- administering of the suspected drug in cases where it is re-prescribed;

– exclude other diseases/causes of liver injury or exacerbation/relapse of a pre-existing liver disease [45].

• In the absence of an obvious relationship between drug intake and liver damage, **it is recommended** to use the RUCAM scale (see Appendix D1) and its modifications to establish causality [109, 111, 147–152].

Grade of recommendation – B; level of evidence – 2.

Comments. To decide whether to continue or withdraw treatment, a number of scales have been developed [153–155], among which the optimal one is the Roussel-Uclaf Causality Assessment Method (RUCAM) under the auspices of CIOMS (1989) [109, 111], which also serves as both professional and legal protection in the further management of the patient [145]. In 2022, a modified electronic version was proposed – RECAM (Revised Electronic Causality Assessment Method – revised electronic method for assessing the causality of drug-induced liver injury, https://dilirecam.com), presumably more reproducible and reliable than RUCAM [151]. The RUCAM and RECAM systems should not be used as the sole diagnostic tool for DILI [13]. Their reliability is reduced by the simultaneous use of several medications or dietary supplements; treatment with herbal products or dietary supplements with an incompletely defined composition; on the ALF and/or exacerbation of the underlying liver disease. RUCAM is not applicable to assess cases with severe or fatal outcomes after discontinuation of the suspected drug [156–160].

• If DILI is suspected, **it is recommended** to compare the patient's clinical and laboratory data with published information on the hepatotoxicity of the suspected drug to identify causality (Fig. 1 in Appendix B) [14, 42, 161, 162].

Grade of recommendation – C; level of evidence – 5.

Comments. Causality analysis between drug intake and liver damage, especially in complex cases, requires a comparison of the type and phenotype of damage with published data, electronic resources containing information on registered cases of DILI and their characteristics, for example, LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/). In complex diagnostic cases, to confirm DILI and determine the causal interrelations with the suspected agent (drug, dietary supplement, herbal product), it is necessary to obtain an expert opinion – this is the gold standard for diagnostics (Table 5 in Appendix A3) [1, 2, 4, 13, 163, 164].

2.5.2. Assessment of DILI prognosis

According to the DILIN registry, DILI directly or indirectly lead to death in 7.6 % of registered cases, with ALF being the main cause of death [20].

A meta-analysis of 12 studies including 4290 patients showed that the rates of ALF and liver-related death are similar in cholestatic and hepatocellular DILI, with the cholestatic pattern of DILI more often leading to chronicity [165]. Death from ALF typically occurs within 6 months of initial drug exposure [145]. Analysis of data from various DILI registries has identified a number of factors predisposing to adverse outcomes: female gender, ethnicity, advanced age, underlying liver disease, and comorbidities [95, 166–168]. A number of laboratory parameters (high levels of hyperbilirubinemia, leukocytosis, hypoalbuminemia, thrombocytopenia, coagulopathy) are associated with mortality in DILI [20, 168]. Histological features also have prognostic significance: extensive necrosis and ductular reaction were shown to be associated with a higher risk of mortality, while the presence of eosinophils in the infiltrate and granuloma was a predictor of spontaneous recovery [47].

Revealed risk factors help predict worsening to severe DILI. Early identification of patients at high risk of adverse outcomes helps optimize a clinical approach. For example, patients with hepatocellular DILI and jaundice require hospitalization and careful laboratory monitoring due to the high risk of adverse outcomes.

• **It is recommended** to evaluate the prognosis of patients with hepatocellular DILI using Hay's law (or its modification) to detect the risk of ALF and an adverse outcome timely [11, 169, 170].

Grade of recommendation – B; level of evidence – 2.

Comments. In its classical form, Hay's law [160] consists of three provisions: the drug causes hepatocellular damage (an increase in serum ALT or AST activity > 3 ULN); increased serum total bilirubin > 2 ULN without signs of cholestasis (ALP activity in the blood < 2 ULN); absence of other reason explaining combination of increased ALT and total bilirubin elevation. Hay's law has been validated [168, 170, 171], it has high specificity and negative predictive value, but low sensitivity [172]. Hay's law is not applicable to patients with initial cholestatic and mixed DILI. A modification (new Hay's law) has been

developed: serum total bilirubin ≥ 2 ULN in combination with nR > 5, where nR = (serum ALT or AST level, whichever is higher/ULN) ÷ (ALP level/ULN), which better identifies the risk of death within 26 weeks [172]. A number of new predictive models have been proposed [172–178].

• **It is recommended** to calculate the MELD (or its modifications) in patients with DILI and liver failure to assess the prognosis and define a clinical approach (see Appendix A3) [20, 178–180].

Grade of recommendation — A;
level of evidence — 1.

Comments. In patients with DILI, MELD > 19 is associated with the risk of death within 26 weeks [20] and effectively predicts mortality within 1 year [178]. Importantly, MELD ranks patients on the LT waitlist. Modifications of MELD-Na and MELD 3.0 are currently used in transplantology, but their diagnostic value in DILI has not been studied. Combinations of MELD with individual laboratory parameters are being studied [181].

• **It is recommended** to consider using the Royal College criteria and/or the ALF Study Group survival prediction model for prognosis assessment in patients with DILI and paracetamol**-induced ALF, when deciding on treatment strategy (see Appendix A3) [179, 182].

Grade of recommendation — B;
level of evidence — 2.

Comments. ALF is defined as impaired coagulation (INR > 1.5) and any degree of mental retardation (MIT) in a patient without previous cirrhosis and with a disease duration of less than 26 weeks [183]. A number of scales have been developed to assess short-term survival [184–186], the most studied of which are the King's College Hospital criteria (KCHC) [184] and the ALF Study Group short-term transplant-free survival prediction model [182] (Appendix A3). When deciding on emergency LT in paracetamol**-induced ALF, the MELD should not replace specific scales [179].

3. Treatment, including drug and non-drug therapies, diet therapy, pain relief, medical indications and contraindications for the use of treatment modalities

3.1. Non-pharmacological treatment

Although discontinuation of a suspected drug (or dietary supplement, or herbal product) is a critical step in the treatment of patients with DILI [14, 187], it is always necessary to analyze clinical and laboratory data and the circumstances associated with the use of the suspected drug. This will also help avoid unjustified drug discontinuation:

1. If the ALT level increases less than 3 ULN (or the average value with initially elevated ALT), and there are no other signs of liver damage (clinical, laboratory, instrumental, morphological), it is advisable to consider continuing therapy [188–191]. Furthermore, the phenomenon of drug adaptation has been well described — an asymptomatic transient increase in ALT and AST upon drug initiation, which is temporary and disappears with continued administering [190–192].

2. If the ALT level increases by more than 3 ULN (or baseline) due to a drug, in the absence of other clinical or laboratory signs of liver damage, the drug should be discontinued (or its dose modified, if acceptable) [188, 193, 194]. An increase in ALT activity more than 3 ULN is considered a possible predictor of the development of DILI, determining the need to discontinue the drug [194, 195]. Exceptions include certain drugs with a high risk of hepatotoxicity (such as antitumor drugs), for which specific criteria for acceptable deviations in liver function parameters have been developed. [196].

• **It is recommended** to discontinue the suspected drug in patients with presumed and proven DILI, to prevent the risk of developing an adverse outcome, except in cases where it is vital for the patient and there is no alternative [14, 187].

Grade of recommendation — C;
level of evidence — 5.

Comments. It is assumed that in idiosyncratic DILI, early discontinuation of the suspected drug prevents the progression of liver damage and more than 80 % of patients fully recover [13, 94], however, approximately 10 % have a high risk of an adverse outcome [2].

• **It is recommended** that patients with suspected and proven DILI discontinue dietary supplements and herbal products in order to prevent the risk of developing an adverse outcome [187].

Grade of recommendation — C;
level of evidence — 5.

• In situations where the suspected drug is vital and there is no alternative, in order to prevent the risk of an adverse outcome in patients with suspected and proven DILI, when deciding on its cancellation, **it is recommended** to be guided by the following criteria:

– increased serum ALT or AST activity > 8 ULN;

– increased serum ALT or AST activity > 5 ULN for more than 2 weeks;

– increased serum ALT or AST activity > 3 ULN and total bilirubin level > 2 ULN or INR > 1.5;

– increased serum ALT or AST activity > 3 ULN in combination with clinical symptoms (weakness, nausea, vomiting, pain or tenderness on palpation in the right upper quadrant of the abdomen, fever, rash and/or eosinophilia) [14, 187, 197].

Grade of recommendation – C;
level of evidence – 5.

Comments. The FDA criteria for discontinuing drugs in clinical trials developed in 2009 were subsequently used in practice guiding whether to continue strongly indicated drug in the presence of DILI [14, 187]. For some medications with high hepatotoxic potential and for particular situations, specific recommendations have been developed to decide whether to continue or discontinue treatment (for example, in antitumor therapy) [196, 198].

3.1.1. Non-pharmacological treatment of DILI due to antitumor medications

Idiosyncratic or indirect DILI, most frequently encountered in oncology practice, typically require dose reduction of anticancer chemotherapy drugs or their complete temporal or sometimes permanent discontinuation. The National Cancer Institute's criteria for the severity of hepatotoxicity (Appendix D2) and the Hay's Law criteria [196, 197] assist in decision-making. However, specific guidelines have been developed for a number of pharmacological groups of anticancer drugs, which are presented below.

• To prevent life-threatening conditions due to suspected or proven DILI in patients receiving antitumor therapy, **it is recommended** to modify the dose or discontinue the suspected drug, following the criteria developed for the specific drug (if available; see Table 6 in Appendix A3) [196, 199, 200].

Grade of recommendation – C;
level of evidence – 5.

Comments. Full information is provided in the instructions for use of each drug or on the website of the State Register of Medicines (https://grls.rosminzdrav.ru) [196, 199, 200], as well as in the clinical guidelines for each group of oncological diseases presented in the rubricator of the Ministry of Health of the Russian Federation [201].

• To prevent the risk of an adverse outcome in patients with DILI due to antitumor drugs of the ICI class, **it is recommended** to modify the dose or cease the suspected drug, being guided be the degree of hepatotoxicity according to the US National Cancer Institute scale (Appendix D2): 1) for Grade 2 (G2), temporarily discontinue treatment until reaching G1; 2) for Grades 3–4 (G3–4), permanently discontinue treatment until reaching G2 [202, 203].

Grade of recommendation – B;
level of evidence – 3.

Comments. It is generally accepted that the development of Grade 2 hepatotoxicity requires temporary discontinuation of the suspected drug, with possible rechallenge if laboratory dynamics are positive. In the case of Grade 3–4 hepatotoxicity, rechallenge with the suspected drug is inappropriate [204]; however, this issue continues to be studied [205]. Principles for treating hepatotoxicity in patients with cancer are outlined in the RUSSCO practical guidelines.

3.2. Pharmacological therapy

The use of drugs for the treatment of liver and biliary tract diseases (hepatotropic agents) in DILI is aimed at minimizing the need to discontinue the vital suspected drug, reduce its dosage, and delay therapy. There are no universal drugs that can be effectively used in the treatment of all forms of DILI [1, 13]. Conditionally, pharmacological agents used in DILI can be divided into two groups:

1) specific agents, effective in damage caused by a specific drug – acetylcysteine** (for damage caused by paracetamol**), #levocarnitine (for damage caused by valproic acid**);

2) drugs that are effective in specific patterns or phenotypes of DILI – glucocorticoids (GC), hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases).

3.2.1. Pharmacological therapy of DILI with drugs that have a specific action

• **It is recommended** to administer acetylcysteine** parenterally at 150 mg/kg over 15 minutes, then 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours to patients with paracetamol-induced liver injury** to improve the prognosis [206–208].

Grade of recommendation – A;
level of evidence – 3.

Comments. Action of acetylcysteine**: reduction of formation of reactive oxygen species and compounds [209, 210], reduction of expression of Toll-like receptors 2 and 4 and TNF-α [211] and activation of guanylate cyclase [212]. In paracetamol**-induced DILI, two regimens of acetylcysteine** administering are used: 1) an intravenous 21-hour regimen (see above); 2) an oral 72-hour regimen with a loading dose of 140 mg/kg, then 70 mg/kg every 4 hours (up to 72 hours), providing a 40 % survival rate without liver failure compared to placebo – 27 % [2, 208, 213].

Intravenous administering is preferable in case of vomiting, gastrointestinal diseases, liver failure, pregnancy [214, 215]. In cases of massive paracetamol** poisoning, the dose of acetylcysteine** may be increased to 200 mg/kg over 16 hours [213, 216]. Time for optimal initiation of treatment with acetylcysteine** is no more than 24 hours after paracetamol** poisoning (the difference in mortality is 28 %) [206]. The main evidence for the effectiveness of acetylcysteine in treatment and prevention of DILI is presented in Table 7 in Appendix A3.

• To improve the prognosis in patients with DILI caused by valproic acid**, **it is recommended** to administer #levocarnitine once intravenously by drip at a dose of 100 mg/kg (but not more than 6 g) with an infusion rate of 30 minutes, followed by intravenous drip infusion at a dose of 15 mg/kg every 4 hours until the patient's condition stabilizes [1].

Grade of recommendation — C;
level of evidence — 5.

Comments. Levocarnitine regulates the transport and metabolism of acetyl coenzyme A, which is necessary for plastic and energy metabolism, detoxification of xenobiotics, and has an anti-apoptotic effect [217]. Levocarnitine is prescribed for DILI with valproic acid** against the background of a decreased level of consciousness and/or hyperammonemia. Duration — until clinical improvement, a decrease in the level of ammonia in the blood (if initially elevated) or the appearance of side effects of levocarnitine [218, 219]. The result is 40 % increase in survival. Parenteral administering of the drug is more effective than oral [220, 221]. There is evidence of a positive effect of levocarnitine on hepatotoxicity in therapy with pegaspargase** [222, 223].

The main evidence of the effectiveness of #levocarnitine for the treatment and prevention of DILI is presented in Table 7 in Appendix A3.

3.2.2. Pharmacological therapy for specific patterns or phenotypes of DILI

Ursodeoxycholic acid** (UDCA**) and the spectrum of its application in DILI

UDCA** stimulates the cellular efflux of toxic lipophilic fatty acids, promotes their detoxification, and has an anticholestatic effect. The drug directly neutralizes reactive oxygen species, induces the synthesis of acetylcysteine and glutathione, stimulates the antioxidant and anti-inflammatory pathways of the transcription factor NRF2, prevents the activation of nuclear factor kappa-B (NF-κB), and slows hepatocyte apoptosis [224, 225]. The possibility of using #UDCA** in DILI is considered by a number of professional societies and systematic reviews, usually at a dose of 10–15 mg/kg/day (in 2–3 doses) orally for up to 6–12 months or more in the absence of severe liver failure [2, 224, 226, 227]. No correlation was found between increasing doses of the drug and therapeutic efficacy [228, 229]. It affects both the severity of cholestasis and the hepatocellular pattern of damage [227].

• **It is recommended** to consider prescribing #UDCA** at a dose of 10–15 mg/kg/day to patients with DILI during antibacterial pharmacotherapy to improve clinical and laboratory parameters of the liver and maintain planned antibacterial therapy protocols in the absence of severe liver failure [224, 225, 227].

Grade of recommendation — C;
level of evidence — 5.

Comments. The use of UDCA** (750–1500 mg daily) in DILI during anti-tuberculosis pharmacotherapy improves the profile of liver markers (ALT, ALP, TBl) compared to the control [230]. In the description of cases and case series of cholestatic and hepatocellular DILI (against the background of amoxicillin + clavulanic acid**, azithromycin**, rifampicin**, isoniazid**, pyrazinamide** therapy), the use of UDCA** in doses of 10–40 mg/kg/day led to a complete or partial improvement in clinical and laboratory parameters of the liver in periods of 2 to 5 months after the start of treatment with the drug [224, 229].

• **It is recommended** to consider the use of #UDCA** in patients with DILI during antitumor or immunosuppressive chemotherapy to improve clinical and laboratory parameters of the liver and maintain planned pharmacotherapy protocols in the absence of severe liver failure [224, 225, 227, 231].

Grade of recommendation — C;
level of evidence — 3.

Comments. In the description of cases and case series of cholestatic and hepatocellular DILI (associated with flutamide**, methotrexate**, capmatinib, pembrolizumab**, nivolumab**, leflunomide**, etc. therapy), the use of UDCA** in doses of 10–40 mg/kg/day led to a complete or partial improvement in clinical and biochemical parameters of the liver within 2 to 5 months from the start of treatment [224]. In a comparative RCT, the use of UDCA** at a dose of 20 mg/kg/day for 8 weeks in rheumatological patients with DILI during methotrexate** therapy had a positive effect on liver chemistries (ALT, AST, ALP, TBL) and the degree of impairment of liver detoxification function (according to the ^{13}C-methacetin

breath test). The dose of 20 mg/kg was more effective than the dose of 15 mg/kg/day [231].

• **It is recommended** to consider prescribing UDCA** at a dose of 10–15 mg/kg/day to patients with severe itching associated with cholestatic DILI in the absence of severe liver failure [2, 224].

Grade of recommendation – C;
level of evidence – 5.

Comments. UDCA** at doses of 750–900 mg daily reduced the severity of pruritus in DILI associated with antiandrogens, anabolic steroids, and systemic antimicrobials within 10 days to 1 month [232–235]. In severe refractory cholestatic skin pruritus in DILI, GCs (1 mg/kg/day or 40 mg daily) can be prescribed as second-line therapy; their effectiveness has been demonstrated in case series [236]. The main evidence for the efficacy of UDCA** for the treatment and prevention of DILI is presented in Table 7 in Appendix A3.

*Ademetionine** and the spectrum of its use in DILI*

Ademetionine** (S-adenosylmethionine) is a precursor of glutathione, inhibits cytochrome CYP2E1, suppresses the expression of TNF-α, induces the production of anti-inflammatory interleukin (IL) 10, has anticholestatic, antiapoptotic, and antifibrogenic effect [237, 238]. The ability of ademetionine** to act as an anticholestatic agent has been demonstrated in RCTs and recommendations of some professional associations [239, 240]. Domestic studies indicate the effectiveness of the substance also in case of mixed DILI phenotype [241].

• In patients undergoing antitumor or immunosuppressive pharmacotherapy (methotrexate**, GC), who have developed DILI, **it is recommended** to consider prescribing ademetionine** to improve clinical and laboratory parameters of the liver, reduce hepatogenic weakness and maintain planned treatment protocols [239, 241–243].

Grade of recommendation – C;
level of evidence – 4.

Comments. The use of ademetionine** in chemotherapy-induced DILI demonstrated a significant ($p < 0.05$) reduction in the levels of TBL, ALT, AST, and GGT by day 14 [241] with the most pronounced anticholestatic effect. The reduction in hepatogenic weakness/fatigue and the antidepressant effect persists for several months after completion of therapy [243, 244]. In the cholestatic type of DILI (often associated with methotrexate** and GC), a course of ademetionine** (2 weeks parenterally and 4 weeks orally) led to positive clinical and laboratory dynamics [245]. In cholestatic, hepatocellular, or mixed patterns of DILI induced by antitumor drugs, ademetionine** is used at a dose of 800 mg daily (or 5–12 mg/kg/day) parenterally for 2 weeks, followed by oral administering of 800–1600 mg daily for up to 1–6 months. In cholestatic or mixed liver damage, combined use of ademetionine** with UDCA** (15–20 mg/kg/day) is possible until cholestasis resolves [198, 246].

• **It is recommended** to consider prescribing ademetionine** to patients with DILI during antibacterial pharmacotherapy to improve clinical and laboratory parameters of the liver and maintain planned antimicrobial treatment protocols [247].

Grade of recommendation – B;
level of evidence – 2.

Comments. In DILI associated with pharmacotherapy for pulmonary tuberculosis, the use of ademetionine** at 400 mg daily parenterally led to an improvement in the antioxidant status of the blood [248]. In a single-center RCT in 180 patients with pulmonary tuberculosis and DILI during anti-tuberculosis therapy (in 83.9 %, four first-line etiotropic drugs were used), the administering of a similar course of ademetionine** reduced cholestasis markers (TBL, GGT) to a greater extent and cytolysis (AST, ALT) to a lesser extent [247]. The main evidence of the effectiveness of ademetionine** for the treatment and prevention of DILI is presented in Table 7 in Appendix A3.

Phospholipids and the spectrum of their application in DILI

The use of phospholipids (phosphatidylcholines) in DILI is justified by their ability to induce endogenous antioxidants (hemoxygenase-1, superoxide dismutase), to help reduce oxidative damage to hepatocyte membranes, their organelles and membrane-associated structures, exerting an antioxidant and anticytolytic effect [249, 250]. The use of phospholipids in anticancer chemotherapy appears promising. In a retrospective study of 98 patients with stage IV gastric cancer treated with either oxaliplatin** (SOX) or oxaliplatin** and capecitabine** (XELOX) and who had a liver failure before treatment or developed severe liver damage after 1–2 cycles of chemotherapy, the use of phospholipids during chemotherapy increased 6-month progression-free survival and revealed a significant correlation between phospholipid treatment and the disease control rate (DCR) (univariate analysis, $p = 0.021$; multivariate analysis, $p = 0.044$) [251].

• **It is recommended** to consider administering phospholipids to patients with DILI associated with antibacterial chemotherapy to improve

clinical and laboratory parameters of the liver and maintain planned antibacterial treatment protocols [240, 252].

Grade of recommendation — C;
level of evidence — 4.

Comments. A 3-year retrospective multicenter study (183 patients) of parenteral use of phospholipids (5–10 mL/day for mild DILI, 10–20 mL/day for severe, and 30–40 mL/day for critical) showed that 34.97 % of patients achieved normal ALT levels and 40.98 % achieved normal AST levels [252]. A meta-analysis of 32 RCTs demonstrated the possible influence of phospholipids to TBL level in DILI [253]. Phospholipids are mainly used for the hepatocellular pattern of DILI at a dose of 250–1000 mg daily (5–20 mL) parenterally for up to 7–10 days, followed by 1800 mg daily orally divided into 3 doses per day for 4 to 12 weeks for the hepatocellular DILI [14].

• **It is recommended** to consider the administering of phospholipids to patients with DILI associated with hormone pharmacotherapy with gestagen or gestagen-estrogen drugs during pregnancy to improve clinical and laboratory parameters of liver [254].

Grade of recommendation — B;
level of evidence — 3.

Comments. Phospholipids can be used during pregnancy. Their parenteral use (250 mg daily (5 mL) for 7–10 days), followed by an oral administering (a total of 1800 mg daily divided into 3 doses per day for 2–3 weeks) in patients with DILI, exposed to progestogen or progestogen-estrogen agents during the first trimester of pregnancy, reduced transaminase activity by 58 % after 4 weeks of treatment, in contrast to 28.2 % in the control group [254].

• **It is recommended** to consider prescribing a fixed combination of glycyrrhizic acid + phospholipids** to patients with DILI during antituberculosis and anti-tumor therapy to improve clinical and laboratory parameters of liver condition [255–257].

Grade of recommendation — C;
level of evidence — 5.

Comments. In DILI occurred in patients with psoriasis receiving methotrexate**, parenteral administering of a combination of glycyrrhizic acid (200 mg daily) + phospholipids (500 mg daily)** for 10 days followed by glycyrrhizic acid (210 mg daily) + phospholipids (390 mg daily)** orally for up to 2 months improved laboratory parameters of the liver [256]. This combination, when administered parenterally (twice a week for 1 month) and followed by oral administering, led to ALT decrease in DILI associated with anti-tuberculosis chemotherapy (isoniazid**, rifampicin**, pyrazinamide**, ethambutol**, ofloxacin**, kanamycin**) [257]. In women with DILI due to treatment of breast cancer with trastuzumab**, doxorubicin**, and paclitaxel**, the use of the combination daily for 2 weeks and then 3 times a week with the addition of 750 mg daily of UDCA** for the period of anticancer therapy ensured normalization of ALT, AST, and bilirubin [255]. The incidence of adverse reactions to fixed combinations of glycyrrhizic acid (glycyrrhizic acid + phospholipids**, glycyrrhizic acid + #UDCA**) is < 10.6 % [258]. The main evidence for the efficacy of phospholipids in treatment of DILI with established specific etiology is presented in Table 7 in Appendix A3.

Ornithine and the spectrum of its application in DILI

Ornithine is a rate-limiting intermediate of the ornithine cycle and an indirect precursor of endogenous antioxidants and polyamines necessary for maintaining the structural integrity of cells and cell cycle progression. Through conversion to arginine and subsequent release of nitric oxide, ornithine improves hepatic microcirculation [259, 260].

• **It is recommended** to consider the use of ornithine for treatment of patients receiving antitumor therapy if they develop DILI with latent or overt HE.

Grade of recommendation — C;
level of evidence — 4.

Comments. Ornithine therapy (L-ornithine-L-aspartate, LOLA) at a dose of 9 g/day for 8 weeks was effective in stopping HE that developed in the context of DILI in 105 patients with ovarian and breast cancer receiving chemotherapy; in the treatment of minimal HE in the context of DILI in patients with rheumatoid arthritis who had been receiving methotrexate for more than 5 years** [261]. In DILI with signs of liver failure and HE associated with chemotherapy for hematological malignancies, ornithine supplementation led to the resolution of HE, a decrease in asthenic syndrome, and a decrease in the values of ALT, AST, ALP, GGT, TBL, and prothrombin time. The drug was administered once intravenously by drip at a dose of 10–20 g/day over 8–14 days, then orally at a dose of 9–18 g/day for 2–4 weeks or longer [262].

• **It is recommended** to consider the administering of ornithine to patients with DILI exposed to antitumor chemotherapy to improve clinical and laboratory parameters of the liver and maintain planned antitumor therapy protocols [264].

Grade of recommendation — C;
level of evidence — 4.

Comments. In patients with stage 1–2 hepatotoxicity according to the NCCN (National Comprehensive Cancer Network), the use of ornithine (LOLA) at a dose of 15 g/day orally for 20 days led to normalization of the sleep rhythm, a decrease in asthenic syndrome, a decrease in ALT, AST, bilirubin, GGT, alkaline phosphatase, and led to a decrease in the number of compelled changes in chemotherapy protocols [264]. In another study, taking ornithine (LOLA) at a dose of 15 g/day for 8 weeks led to an improvement in cognitive functions [265].

• According to the "Liver Cirrhosis and Fibrosis" Guidelines, **it is recommended** to prescribe ornithine to patients with DILI developed over pre-existing liver disease and with the onset or worsening of latent or overt HE for improving prognosis [266].

Grade of recommendation — C;
level of evidence — 5.

Comments. The route of administering of the drug, its dose, and duration of treatment should be selected by the physician in accordance with the "Liver Cirrhosis and Fibrosis" Guidelines [266]. The main evidence for the effectiveness of ornithine for the treatment of DILI of established specific etiology is presented in Table 7 in Appendix A3.

Fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** and the spectrum of its application in DILI

The drug's action is primarily aimed at correcting mitochondrial dysfunction, which is one of the important pathogenetic factors in the development of DILI. Since the drug is a balanced infusion solution, it exerts a volume-dependent detoxifying effect [267–269].

• In patients with DILI, who have been exposed to anti-tuberculosis and anti-Helicobacter pharmacotherapy, **it is recommended** to consider prescribing a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** (400 mL intravenously for 10 days) to improve clinical and laboratory parameters of the liver and maintain planned antibacterial treatment protocols [247, 270, 271].

Grade of recommendation — B;
level of evidence — 2.

Comments. A fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** is effective in the treatment of DILI during tuberculosis therapy (normalization of ALT, AST, GGT, ALP and bilirubin activity in the blood) [247, 272–275] and anti-Helicobacter therapy [276]. In DILI caused by systemic antibacterial drugs and NSAIDs, the use of a fixed combination of 400–800 mL/day for 14 days allowed for the normalization of ALT, AST and GGT levels, surpassing the control group on standard detoxification therapy [277].

• In patients with DILI exposed to antitumor chemotherapy, **it is recommended** to consider the use of a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** to improve clinical and laboratory parameters of the liver and maintain planned antitumor therapy protocols [271, 278, 279].

Grade of recommendation — B;
level of evidence — 3.

Comments. In cancer patients, a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** reduces the level of elevated liver chemistries and improves the quality of life by increasing indicators of social and physical activity, and mental health [278, 280–282]. In patients with hepatocellular, cholestatic or mixed pattern of DILI, exposed to antitumor chemotherapy, the drug can be administered parenterally at a dose of 400–800 mL/day by intravenous drip infusion over 4–12 days [198]. Preclinical studies have shown the absence of its effect on tumor growth and additivity in relation to some antitumor drugs (for example, gemcitabine**) [283].

• In patients with DILI, developed during pharmacotherapy with antipsychotic drugs, **it is recommended** to consider prescribing a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** to improve clinical and laboratory parameters of liver function and maintain planned antipsychotic therapy protocols [271, 284].

Grade of recommendation — B;
level of evidence — 2.

Comments. In a study involving 60 patients with mixed DILI treated with antipsychotics (haloperidol**, trifluoperazine**), the use of a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** (400 mL/day intravenously by drip for 12 days) improved liver function tests, quality of life (SF-36 questionnaire) due to physical functioning and general condition without affecting emotional and social functioning [284]. The main evidence for the effectiveness of the combination of inosine + meglumine + methionine + nicotinamide + succinic acid** for the treatment and prevention of DILI of established specific etiology is presented in Table 7 in Appendix A3.

Bicyclol and its spectrum of application in pulmonary leukemia

Bicyclol is a synthetic compound based on lignanschisandrin C, obtained from Schisandra chinensis (Turcz.) Baill. In DILI, it increases the expression of proteins necessary for autophagy (HSPs — heat shock proteins, AMPK — AMP-activated protein kinase), as well as the activity of antioxidant, anti-inflammatory and anti-apoptotic pathways of the transcription factor NRF2 [285–289].

• **It is recommended** to consider prescribing #bicyclol to patients with hepatocellular and mixed pattern of DILI, who have been exposed to antitumor chemotherapy, to improve hepatic clinical and laboratory parameters and maintain planned antitumor therapy protocols [198, 290].

Grade of recommendation — C;
level of evidence — 5.

Comments. The use of #bicyclol orally at a dose of 75–150 mg daily (in 3 doses) for 3–6 months, as demonstrated to be effective in the treatment of DILI induced by antitumor drugs, is approved by the Russian Society of Clinical Oncology (RUSSCO) [198].

• In patients with DILI, developed during pharmacotherapy with HMG-CoA reductase inhibitors (statins), **it is recommended** to consider prescribing #bicyclol 75 mg daily orally to improve clinical and laboratory parameters of liver function and maintain planned lipid-lowering therapy protocols [291].

Grade of recommendation — B;
level of evidence — 2.

Comments. A multicenter RCT demonstrated the efficacy and safety of bicyclol in statin-induced DILI (atorvastatin** and simvastatin**). The study involved 168 patients with elevated ALT within 2–5 ULN, who were prescribed bicyclol at 75 mg daily (in 3 doses) for 2 or 4 weeks. A decrease in ALT ($p < 0.01$) was observed after both 2- and 4-week therapy. After a 4-week course of treatment, normalization of ALT activity was observed in 74.68 % of patients [291].

• In patients with DILI against the background of anti-tuberculosis pharmacotherapy, **it is recommended** to consider prescribing #bicyclol to at 75–150 mg daily orally for up to 8 weeks to improve clinical and laboratory hepatic parameters and maintain planned antibacterial therapy protocols [292–294].

Grade of recommendation — B;
level of evidence — 2.

Comments. The use of bicyclol in patients with acute DILI, developed during antituberculosis therapy, allowed to reduce the ALT level, especially in the group receiving a higher dose [294, 295]. The drug is effective primarily in the hepatocellular or mixed pattern of idiosyncratic DILI [292, 296]. In idiosyncratic DILI, ALT reduction is more effective with a bicyclol dose of 150 mg daily ($p < 0.001$) (already in the first week) than with a dose of 75 mg daily (the median time for ALT normalization is 29 and 16 days, respectively) [296]. The main evidence of the effectiveness of bicyclol for the treatment and prevention of DILI of established specific etiology is presented in Table 7 in Appendix A3.

Morpholinium Thiazotate and its spectrum of application in DILI

Morpholinium thiazotate acts as a scavenger of reactive oxygen and nitrogen species, slows the consumption of endogenous antioxidants, and inhibits proinflammatory macrophage polarization and apoptotic reactions [297–300]. Its ability to suppress the production of nitrotyrosine and peroxynitrite is significant for both liver and cardiovascular damage [301, 302].

• **It is recommended** to consider the use of morpholininium thiazotate in patients with DILI, associated with antibacterial chemotherapy, to improve clinical and laboratory parameters of the liver and maintain planned antibacterial therapy protocols [301, 303, 304].

Grade of recommendation — C;
level of evidence — 3.

Comments. Morpholinium thiazotate turned out to be effective in patients receiving prolonged antibacterial therapy, reducing transaminase activity and the TBL level ($p < 0.05$) [301]. It is capable of potentiating the effect of combination hepatotropic therapy and reducing the severity of DILI (based on ALT, AST, ALP, GGT, TBL) and oxidative stress during anti-tuberculosis treatment [304]. The drug in the form of morpholinium salt of thiazotic acid is usually used at a dose of 100 mg daily (intravenously) or 100–150 mg daily (intramuscularly) for up to 5 days, followed by a transition to oral administration of morpholinium thiazotate at a dose of 600–800 mg daily in 3–4 doses for up to 30 days for hepatocellular and mixed types of DILI [301]. The main evidence of the effectiveness of morpholininium thiazotate for the treatment and prevention of DILI of established specific etiology is presented in Table 7 in Appendix A3.

Combined use of hepatotropic drugs (ATC code A05, drugs for the treatment of liver and biliary tract diseases) in DILI

There are certain pathogenetic justifications for the combined use of a number of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the form of both non-fixed and fixed combinations, which allow for the

expansion of the spectrum of their hepatotropic action [272, 305]. In mixed pattern DILI, it is possible to use dual combinations of hepatotropic agents (A05, drugs for the treatment of liver and biliary tract diseases), one of which is effective against the hepatocellular pattern of injury, and the other — against the cholestatic pattern. The use of two drugs with anti-inflammatory action and targeting the hepatocellular pattern of damage is not considered rational [45]. In cholestatic or mixed liver damage, a combined use of ademetionine** with UDCA** is possible until cholestasis resolves [198, 306, 307]. Data on the successful combined use of GC with UDCA** in DI-ALH and liver injury on the background of ICI treatment have been obtained [308, 309]. The possible use of combination of phospholipids and bicyclol [310], acetylcysteine** with other drugs for the treatment of liver diseases [311], UDCA** and tocopherol [312], UDCA** and a fixed combination of glycyrrhizic acid + phospholipids** [257] in DILI has been demonstrated. The details of using a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** are discussed above.

3.2.3. Pharmacotherapy of some DILI phenotypes

Pharmacotherapy of DI-ALH

• **It is recommended** to use prednisolone** at a dose of 0.5–1 mg/kg/day orally for treatment of DI-ALH until the laboratory parameters of the liver are normalized, with subsequent dose reduction and gradual discontinuation of GC [14, 90, 313–315].

Grade of recommendation — B;
level of evidence — 3.

Comments. GCs affect the function and interaction of immune cells, proinflammatory cytokine signaling pathways, and apoptosis [316, 317]. There are no studies with specific recommendations for the use of GCs in DI-ALH [58], with the exception of monoclonal antibody-induced DILI [1, 198]. Therapy of such DILI with prednisolone** leads to a more rapid decrease in liver enzymes and a long-lasting, relapse-free therapeutic effect [318–321]. The use of GCs for 6–10 days can reduce liver injury and improve survival in patients with severe DILI with hyperbilirubinemia [322]. If it is impossible to differentiate DI-ALH from AIH, prednisolone** therapy is carried out until the laboratory hepatic parameters are normalized (in DI-ALH, the course is usually 1–2 months), followed by long-term observation of the patient [198, 314, 315]. In severe progressive DILI, immunosuppressive therapy may be considered [323]. A combination of GC and UDCA** may be used in drug-induced cholestatic hepatitis with signs of hypersensitivity (eosinophilia, rash, fever), allowing for a more rapid decrease in bilirubin and transaminase levels in severe DILI [308]. There is limited experience with the use of GC in chronic DILI [324].

Pharmacotherapy of ICI-associated DILI

• **It is recommended** to use prednisolone** orally or #methylprednisolone** (1–1.5 mg/kg/day) parenterally in patients with ICI-associated liver injury for the treatment of immune-mediated hepatotoxicity until normalization of laboratory liver function tests, followed by dose reduction and gradual discontinuation of GC (see Fig. 2 in Appendix B) [2, 198, 325–327].

Grade of recommendation — C;
level of evidence — 4.

Comments. In patients with liver injury associated with ICI therapy, the use of GCs is indicated. Oral administration of 0.5–1 mg/kg/day of prednisolone** is advisable at the ALT level of 3–5 ULN and/or OBIL of 1.5–3 ULN after discontinuation of the suspected drug. If ALT increases to 5–20 ULN and/or TBL to 3–10 ULN or there are signs of liver failure, oral prednisolone** at a dose of 1–2 mg/kg/day or #methylprednisolone** intravenously at a dose of 1–1.5 mg/kg/day is indicated after withdrawal of the suspected drug. Upon positive dynamics in liver chemistries, the GCs dose can be reduced in 4 weeks [198, 325, 328]. The average duration of therapy is 1–3 months [2, 329]. There is no need to exceed the dose of 1.5 mg/kg/day of #methylprednisolone** due to the lack of additional effect [326, 327]. Liver damage sometimes spontaneously resolves without the use of GCs after discontinuation of the suspected drug [330, 331].

• In case of steroid resistance, or insufficient effectiveness, or intolerance to GCs in patients with DILI, associated with the use of ICI, **it is recommended** to prescribe mycophenolate mofetil** (500–1000 mg 2 times a day), tacrolimus** (1.5 mg 2 times a day), azathioprine** (1–2 mg/kg/day), antithymocyte immunoglobulin** (1.5 mg/kg/day), or plasmapheresis (PP) [198, 325, 332–337].

Grade of recommendation — C;
level of evidence — 4.

Comments. In cholestatic liver injury due to ICI accompanied by resistance to GC, the use of UDCA** led to improvement in 81.5 % of patients (average values: drug dose — 10.3 mg/kg, treatment duration — 182.5 days, time to improvement — 39.3 days) [338]. Key principles

for treating hepatotoxicity in patients with cancer are outlined in the RUSSCO practical guidelines, updated annually and available on the website. https://www.rosoncoweb.ru/standarts/suptherapy/2024/.

Pharmacotherapy of hypersensitivity syndrome with liver involvement (DRESS syndrome)

• In patients with hypersensitivity syndrome and liver involvement (DRESS syndrome) **it is recommended** to use #prednisolone** at a dose of 1 mg/kg/day orally until normalization of hepatic laboratory parameters and clinical improvement, followed by a gradual reduction in the dose and discontinuation over 6–8 weeks for the treatment of immune-mediated hepatotoxicity [2, 339–342].

Grade of recommendation – C;
level of evidence – 5.

Comments. The use of prednisolone in DRESS syndrome leads to rapid resolution of the rash, disappearance of fever, and a decrease in liver dysfunction. The total duration of pharmacotherapy with the drug reaches 2–3 months, but in some patients with a high risk of autoimmune complications (diffuse connective tissue diseases, inflammatory bowel disease, etc.) it can be up to a year or longer [339, 343, 344]. The possibility of conducting pulse therapy with methylprednisolone** at a dose of 5–20 mg/kg for 3 days, followed by a slow dose reduction, is being considered; however, the question of the safety of such treatment due to a paradoxical increase in the risk of developing autoimmunity remains open [339].

• In patients with hypersensitivity syndrome with liver involvement (DRESS syndrome), **it is recommended** to prescribe steroid-sparing therapy: cyclosporine** (200 mg daily in two doses for 5 days), or mycophenolate mofetil** (500 mg 2 times/day), or rituximab** (1400 mg/week for 1 month), or cyclophosphamide** (intravenous 750 mg/m^2 with a transition after 11 days to a dose of 100 mg daily orally for 6 months) for the treatment of immune-mediated hepatotoxicity (in case of steroid resistance, relapse or impossibility of using target doses of GC), and to consider the use of PP for treatment [339, 345, 346].

Grade of recommendation – C;
level of evidence – 3.

Pharmacotherapy of DI-SSC

The main pharmacotherapy measures for DI-SSC include the use of GCs (see Section "Pharmacotherapy of hepatitis associated with the use of immune checkpoint inhibitors"). However, steroid resistance may develop in patients with DI-SSC or cholestasis [347–349]. In this case, the use of UDCA** (600 mg daily) in combination with a fibrate may have an additional positive effect on improving liver parameters [309].

Pharmacotherapy of VBDS (chronic cholestasis)

Pharmacotherapy for VBDS has not been developed, but there is some evidence of the effectiveness of using #UDCA** to correct dyslipidemia in this syndrome in doses from 750 mg daily to 30 mg/kg/day with a treatment duration of up to 9 weeks [81, 350, 351].

Pharmacotherapy of sinusoidal obstruction syndrome/veno-occlusive disease of the liver

Sinusoidal obstruction syndrome/veno-occlusive liver disease (SOS/VOD) is a serious complication of hematopoietic stem cell transplantation, as well as exposure to pyrrolizidine alkaloids or some antitumor drugs (oxaliplatin**, gemtuzumabozogamicin, ICT, etc.). The use of UDCA** (12 mg/kg/day or 600 mg daily for 30–90 days) in the primary prevention of SOS/VOD appears promising; treatment with UDCA and some antithrombotic agents is associated with decrease of the incidence of this syndrome (OR = 0.38; 95% CI: 0.14–1.06; SUCRA = 0.720) [352, 353].

Pharmacotherapy of acute liver failure (ALF)

In cases of DI-ALF of specific etiology (for example, caused by an overdose of paracetamol** or the use of valproic acid**), it is necessary to remove the toxicant from the body as quickly as possible and to administer specific antidote therapy to improve the prognosis [1, 2, 354].

In the first 4 hours after paracetamol** intoxication, an intestinal adsorbent can be used to prevent further absorption of the toxicant [355]. The use of acetylcysteine** in such patients at an early stage can prevent the progression of HE (see Section "Acetylcysteine**") [1, 2], and 70 % of patients can avoid the need for LT [356]. The features of the use of #levocarnitine in valproate-induced ALF are described in Section "Levocarnitine".

The main approach to the treatment of DI-ALF of non-specific etiology is the use of extracorporeal detoxification methods (EDM) until liver function is restored [1] (see Section 3.3 "Other treatment"). Although this treatment modality does not affect survival in such patients, it helps them to undergo LT, which allows approximately 80 % of transplant recipients to survive for a year [355]. Maintenance therapy alone without LT is effective in only

10–30 % of patients with DI-ALF of non-specific etiology [346].

The use of acetylcysteine** is possible and is being discussed as a maintenance therapy for non-paracetamol-induced liver injury [357, 358]. The use of the drug in a three-day course in such patients with DI-ALF and non-severe (stages I–II) HE at an initial loading dose of 150 mg/kg/h for 1 h, followed by a transition to a dose of 12.5 mg/kg/h for 4 h and subsequent continuous infusion at a dose of 6.25 mg/kg for 67 h, made it possible to increase transplant-free survival to 52 %, while in the placebo group it was only 30 % ($p = 0.04$) [359, 360].

Treatment with #acetylcysteine** significantly improves survival in patients without LT (55.1 % vs. 28.1 %) and also provides a shorter hospital stay (SMD = –1.62; $p < 0.001$), without affecting overall survival though [361]. However, in cases of DI-ALF due to anti-TB medication, although it significantly reduces the length of hospitalization, it does not affect mortality [362].

Routine use of GCs in idiosyncratic DILI is undesirable [1], but they may be useful in patients with severe DILI who do not respond to traditional treatment [363].

3.3. Surgical treatment

Liver transplantation

• **It is recommended** to consider performing LT in patients with DILI and severe liver failure to prevent fatal outcome [14, 145, 364–366].

Grade of recommendation – C;
level of evidence – 5.

Comments. DILI is the main cause of ALF, which, according to the publications, requires LT in 18 % of cases [181, 367–371]. It is usually performed when conservative management is ineffective [14, 371, 372], as well as in some cases of DILI with the phenotype of VBDS, progressive portal hypertension [2, 14, 20, 373]. In the case of acute severe DILI, the patient's management approach should be discussed jointly with the LT center [374]. Graft and patient survival after LT in ALF due to DILI is lower comparatively to LT performed for other reasons [375–378]. Patients with ALF are assigned Status 1 for LT (Table 9 in Appendix A3).

• **It is recommended** to determine the MELD score (or its modifications) in patients with DILI and ALF, to assess the need for LT [20, 185].

Grade of recommendation – C;
level of evidence – 5.

Comments. The Model for End-Stage Liver Disease (MELD) is the most widely used prognostic tool of 90-day survival in patients with advanced liver disease. Appendix A3 provides calculating formulas. MELD has been shown to effectively predict 1-year mortality and the need for LT in patients with DILI [20, 178].

3.4. Other treatment modalities

EDMs are used in the treatment of patients with liver failure, but the indications for them in DILI are not standardized. Possible mechanisms of action of EDMs in DILI include the removal of exogenous and endogenous toxicants, modulation of the immune response, and replacement of deficient factors [379]. The main situations in which EDMs are considered in DILI include severe, progressive, or fulminant liver damage, lack of response to standard therapy [380, 381], immune-mediated liver injury [280], and before LT [379]. In cases of severe (including immune-mediated) liver injury, EDMs can halt the progression of liver injury and prevent the development of acute liver failure and an unfavorable outcome [205, 382]. According to some data, EDMs are more effective if initiated in the early stage of liver injury, before the development of irreversible changes, and act as salvage therapy in severe liver damage [383]. Before LT, EDMs are used as a bridge technique, which allows to gain time, stabilize the patient's condition, and improve their prognosis before surgery [384].

Currently, the greatest experience with its use has been accumulated with PP (PlasmaExchange, PLEX). In some studies, the use of PP was associated with improved survival in patients with severe forms of DILI, as well as improved clinical and laboratory parameters [385, 386]. A systematic review showed that PP in patients with ALF improves 30- and 90-day LT-free survival [387]. PP can be considered as one of the potential treatment options and should be used in DILI in combination with other treatment options. It is necessary to take into account that PP is associated with fairly serious risks: infections, bleeding, thrombosis, allergic reactions, and electrolyte disturbances. Other EDM options used in ALF, including those due to DILI, include hemodialysis, hemodiafiltration (HDF), selective plasmafiltration, plasmadiafiltration, selective bilirubin absorption in plasma, albumin dialysis using a molecular adsorbent recirculating system (Molecular Adsorbent Recirculating System, MARS) or a fractionated plasma separation and adsorption system (FPSA or Prometheus) [388]. The effectiveness of some

of them has been demonstrated primarily in case series of ALF due to DILI, including those combined with acute kidney injury and severe cholestatic liver disease [389, 390]. There are data on the effectiveness of the albumin dialysis method (e.g., MARS, Prometheus) in patients with DILI, especially with the cholestatic pattern [390–394].

• In patients with DILI with liver failure, cholestatic pattern of DILI with severe clinical symptoms, **it is recommended** to consider EDM (PP, etc.) in order to improve clinical and laboratory parameters, increase patient survival, stop the progression of liver damage, prevent the increase in ARF and unfavorable outcome [205, 379, 382–384, 386, 387, 395–398]. The decision to use EDM is made on an individual basis, and the choice of detoxification modality depends on its availability for a specific medical institution and the parameters of the patient's condition [379].

Grade of recommendation — C;
level of evidence — 5.

Comments. EDM should only be performed by qualified medical personnel in a specially equipped department.

4. Medical rehabilitation and sanatorium-resort treatment, medical indications and contraindications for the use of medical rehabilitation methods, including those based on the use of natural healing factors

Specific measures of medical rehabilitation and sanatorium-resort treatment for patients with DILI have not been developed.

5. Prevention and follow-up monitoring, medical indications and contraindications for the use of prevention methods

Effective prevention of DILI is a systemic program that requires scientifically based control of potentially hepatotoxic drugs by regulatory authorities (suspension of sales or direct recall, revision of instructions for use of drugs, restriction of their use), the establishment of risk management by pharmaceutical companies (pharmacovigilance, development of appropriate surveillance and risk management strategies, active research, revision of instructions for use of drugs and communication of risk information), DILI risk management in clinical practice by specialists (regular monitoring during treatment, early detection of DILI, proper diagnosis, decision to discontinue treatment or reduce the dose of the drug), as well as public education on drug safety and their rational use.

It is important to comply with the requirements for prescribing drugs to prevent DILI: strict adherence to the instructions for the drug (indications and contraindications) and taking into account drug interactions, including the simultaneous use of dietary supplements and herbal products [145, 364, 394].

5.1.1. Primary prevention of DILI

• For primary prevention of DILI, **it is recommended** to assess the patient's drug history and the presence of risk factors for the development of DILI before prescribing potentially hepatotoxic drugs [45].

Grade of recommendation — C;
level of evidence — 5.

Comments. The main risk factors for DILI, associated with some drugs, are described in Table 4 (Appendix A3) and, in some cases, are also noted in the instructions for use of the drug. To obtain information on drug hepatotoxicity and risk factors, physicians should actively use interactive websites such as LiverTox [145, 364].

• **It is recommended** to carry out regular clinical and laboratory monitoring during the administration of drugs with a high risk of hepatotoxicity for the prevention and prompt detection of DILI in patients [45, 90].

Grade of recommendation — C;
level of evidence — 5.

Comments. The monitoring schedule of clinical and laboratory parameters is determined by the type of a drug, instructions for its use, the patient's initial condition and existing risk factors for DILI, as well as the clinical guidelines for the nosologies for which the drug is prescribed. The use of most drugs, known for adverse reactions in the form of hepatotoxicity (specified in the instructions for the drug), it is generally necessary to monitor the liver chemistries (ALT, AST, ALP, bilirubin) in 4–6 weeks intervals, especially during the first 6 months of treatment with the drug [145, 399].

• When prescribing potentially hepatotoxic drugs, **it is recommended** to discuss with the patient the need to immediately inform the doctor about the appearance of new symptoms and/or an increase in the severity of symptoms (such as weakness, jaundice, abdominal pain/discomfort, nausea/vomiting, itching or darkening of urine) in order to promptly identify DILI [13, 400, 401].

Grade of recommendation — C;
level of evidence — 5.

• **It is recommended** that before prescribing potentially hepatotoxic drugs to patients with underlying liver disease, it is necessary to assess its severity, the possible risk of developing DILI, and determine the initial level of the liver chemistries (ALT, AST, ALP, bilirubin) for primary prevention of DILI, its timely diagnosis, and prevention of adverse outcomes [13, 94, 400–402].

Grade of recommendation — C;
level of evidence — 5.

• Before prescribing potentially hepatotoxic drugs to patients with underlying chronic liver diseases and impaired liver function in order to prevent development and adverse outcomes of DILI, **it is recommended** to: a) assess the benefits/risks of therapy; b) make a decision on the use of drugs on an individual basis, balancing the risks and benefits of therapy; c) develop an individual plan for preventive monitoring of liver condition during therapy [13, 364].

Grade of recommendation — C;
level of evidence — 5.

• For the primary prevention of DILI, **it is recommended** to warn patients on the need to notify their physician about the use of dietary supplements and herbal products and to inform patients that dietary supplements and herbal products can be the cause of DILI [13, 90, 364, 403].

Grade of recommendation — C;
level of evidence — 5.

5.1.2. Secondary prevention of DILI

• When DILI is diagnosed, **it is recommended** that the physician make an entry in the medical documentation (medical history, outpatient medical record) indicating the suspected or causative drug (dietary supplement, herbal product) with a description of the adverse reaction and give a patient the medical document to minimize the risk of recurrence of DILI [14, 90, 364, 399].

Grade of recommendation — C;
level of evidence — 5.

Comments. In case of adverse drug reactions, it is mandatory to make a corresponding entry in the patient's medical record, indicating the suspected or causative drug, and provide the patient with medical documentation describing the adverse reaction and the etiologic factor. If an adverse drug reaction (ADR) is detected and its cause is determined, Roszdravnadzor (Federal Service for Surveillance in Healthcare) should be notified by completing the special form "Notification of an Adverse Reaction, Adverse Reaction, or Lack of Expected Therapeutic Effect of a Medicinal Product", available at the Roszdravnadzor website (https://roszdravnadzor.gov.ru/drugs/monitpringlp). Completed forms should be sent to: pharm@roszravnadzor.ru.

• For secondary prevention of DILI, **it is recommended** to inform the patient, who had the condition, about the need to report this to their medical care providers and to present the relevant document, as well as to prevent independent repeated use (without a doctor's prescription) of the causative drug (dietary supplement, herbal product) and to avoid other drugs (dietary supplement, herbal products) of the same pharmacological group to minimize the risk of recurrent DILI [14, 90].

Grade of recommendation — C;
level of evidence — 5.

• It is not recommended to re-prescribe drugs that previously caused DILI to a patient, except in cases where the drug is vital and there is no adequate alternative for secondary prevention of DILI [13, 14, 90].

Grade of recommendation — C;
level of evidence — 5.

Comments. The decision to re-prescribe a medication that previously caused DILI should be made in cases where the benefit of its use outweighs the potential risk of developing severe DILI in this patient within the framework of a medical council or medical commission.

5.2. Follow-up observation

• **It is recommended** to all patients with DILI to undergo a routine examination (checkup, consultation) with a gastroenterologist, and in their absence, a routine observation (examination, consultation) with a general practitioner or a family physician for a dynamic assessment and determination of the duration of follow-up observation [20, 58, 145, 178, 390–392].

Grade of recommendation — C;
level of evidence — 5.

Comments. Based on the approach to follow-up observation, patients with DILI can be divided into three groups: 1) Patients with acute and persistent DILI should be monitored until complete recovery (or achievement of another clinical outcome) [20, 169, 178, 404, 405]. Most often, acute DILI resolves within 6 months after discontinuation of the suspected drug with a good prognosis, but in some patients liver failure or irreversible changes may develop. Patients with the cholestatic pattern of DILI have a higher risk of developing chronic liver damage [20, 169, 178, 404, 405]; 2) Patients with DI-ALH, after its resolution, should be monitored for 3 years with assessment of ALT activity once every 6 months to exclude true AIH [58, 64, 314, 323]. The main difference

of DI-ALH from true AIH is the resolution of DILI after discontinuation of the suspected drug (with or without a short course of GC) and the absence of relapses [314]; 3) Patients with chronic DILI should be monitored depending on the phenotype of DILI, the presence of complications, the scope of their examination is determined on an individual basis [145, 406, 407].

5.3. Pharmacological prevention of DILI

• **It is recommended** to consider prescribing #ademetionine** 400 mg intravenously for 60 days to patients receiving cyclosporine** to prevent the development of DILI [408].

Grade of recommendation — B;
level of evidence — 2.

Comments. A double-blind, randomized, controlled study found that ademetionine** at a dose of 400 mg once a day intravenously for 60 days, in combination with basic psoriasis therapy (cyclosporine**), reliably prevented an increase in the level of transaminases, alkaline phosphatase, and bilirubin ($p < 0,05$) [408].

• In patients receiving antitumor therapy **it is recommended** to consider prescribing #ademetionine** orally at a dose of 800 mg per day divided into two doses during the course of treatment to prevent the development of DILI and maintain planned antitumor therapy protocols [409, 410].

Grade of recommendation — C;
level of evidence — 4.

Comments. In a retrospective study of the efficacy of ademetionine in preventing hepatotoxicity in 105 patients with colorectal cancer receiving adjuvant therapy with FOLFOX (fluorouracil + calcium folinate + oxaliplatin), changes in or discontinuations of the chemotherapy protocol in the group, receiving ademetionine were observed in 14 % of cases, compared to 71 % in the control group [409]. Similar results were obtained in a study of 78 patients with metastatic colorectal cancer receiving chemotherapy using the XELOX (oxaliplatin + capecitabine + bevacizumab) regimen [410].

• In patients receiving antitumor therapy, **it is recommended** to consider the use of a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** (intravenously daily for 5 days, 400 mL per day) to prevent the development of DILI and maintain planned antitumor therapy protocols [198, 279].

Grade of recommendation — B;
level of evidence — 2.

Comments. In a prospective, controlled, open-label RCT of 66 patients with ovarian cancer who received chemotherapy using cisplatin** and carboplatin**, the inclusion of a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** to adjuvant therapy ensured no increase in ALT, AST, and ALP levels [279]. In a study of 145 patients with colorectal cancer who received the FOLFOX and FOLFIRI (irinotecan** + calcium folinate** + fluorouracil**) regimens, the use of this aforementioned fixed combination reduced the hepatotoxicity of the chemotherapy [318]. According to the RUSSCO recommendations, for the prevention of DILI, **it is recommended** to prescribe a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** at a dose of 400 mL intravenously by drip once a day for at least 4 days after each course of chemotherapy to prevent hepatotoxic reactions [198].

• In patients receiving anti-tuberculosis therapy, simultaneously with its start, **it is recommended** to consider oral administration of acetylcysteine** (600 mg 2 times a day) or parenteral administration of ademetionine** (400 mg/day parenterally, 10 days) or a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** (400 mL/day parenterally, 10 days) or morpholinium thiazotate (600 mg/day up to 1 month) to prevent the development of DILI [304, 411–414].

Grade of recommendation — B;
level of evidence — 3.

Comments. In a RCT of tuberculosis patients who were prescribed #acetylcysteine**, no hepatotoxicity was recorded (compared to 37.5 % in the control group) [411]. In another study DILI developed later and laboratory parameters normalized faster after the withdrawal of anti-tuberculosis drugs on the background of #acetylcysteine** therapy [414]. According to a meta-analysis, the administration of #acetylcysteine** significantly reduces the incidence of DILI associated with anti-tuberculosis medication (OR = 0.09), compared to placebo [413].

In RCT, infusion therapy with ademetionine** and a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid** during anti-tuberculosis therapy reduced laboratory parameters of the liver compared to the control group by day 11 of treatment [412].

Concomitant administration of morpholinium thiazotate to patients with pulmonary tuberculosis (TB) prevented DILI in 56.3 %. Furthermore, severe DILI was absent, and the drug's positive effect on oxidative stress and systemic inflammation was demonstrated [304].

• In patients over 60 years of age, receiving antitumor therapy, **it is recommended** to consider prescribing #bicyclol at a dose of 25 mg 3 times a day during the course of chemotherapy to prevent the development of DILI [290, 415].

Grade of recommendation — B;
level of evidence — 2.

Comments. A randomized study included 300 patients over 60 years of age receiving anticancer therapy. The study group prophylactically took #bicyclol at a dose of 25 mg 3 times a day during the course of chemotherapy; the control group did not receive any drugs to prevent DILI. It was found that prophylactic administration of #bicyclol reduced the incidence of DILI in patients to 17.1 % compared to 47.1 % in the control group. The proportion of severe DILI was significantly lower in the prophylactic #bicyclol group compared to the control group (0.7 % and 12.4 % of patients, respectively). An assessment of the drug's effect on the prevention of DILI depending on specific chemotherapy regimens was not conducted [290].

• In patients after kidney transplantation, **it is recommended** to consider the administration of #bicyclol at 75 mg/day for 12 weeks, along with basic therapy, immediately after surgery to prevent the development of DILI [416].

Grade of recommendation — C;
level of evidence — 4.

Comments. The efficacy of #bicyclol in the prevention of DILI due to immunosuppressive therapy for solid organ transplantation was demonstrated in a retrospective cohort study. Patients after kidney transplantation received two regimens: mycophenolate mofetil** + cyclosporine** + prednisolone** or mycophenolate mofetil** + tacrolimus** + prednisolone**. A detailed analysis of the contribution of each drug to the development of DILI was not conducted. 745 cases were included, while 456 patients additionally took #bicyclol 75 mg/day for 12 weeks immediately after surgery. The incidence of DILI in the early postoperative period was significantly lower in the #bicyclol group (4.82 % compared with 20.76 % in the control group, $p = 0.001$) [416].

• **It is recommended** to consider the use of UDCA** at a dose of 375 mg/day for the prevention of DILI in individuals receiving flutamide** [417].

Grade of recommendation — C;
level of evidence — 4.

Comments. A retrospective study evaluated the prophylactic use of 375 mg/day of UDCA in 181 patients with prostate cancer receiving flutamide. ALT elevations were less frequent in patients receiving UDCA, and severe liver injury reported only in the group not receiving the drug [417].

• **It is recommended** to consider prescribing #UDCA** at a dose of 10 mg/kg for up to 7 months for the prevention of DLI in individuals with acne receiving isotretinoin and systemic hormonal contraceptives (combined oral contraceptives) [418].

Grade of recommendation — B;
level of evidence — 2.

Comments. In RCT in women with severe acne (60 patients), the use of UDCA** at a dose of 10 mg/kg for 7 months in combination with isotretinoin and systemic hormonal contraceptives reduced the incidence of increased ALT and AST (5.3 % vs. 63.6 % in the control group), improved the tolerability of pharmacotherapy, and prevented treatment discontinuations (13.6 % in the control group) [418].

• In patients with underlying liver disease, receiving treatment with HMG-CoA reductase inhibitors, **it is recommended** to consider prescribing UDCA** to prevent DILI and enhance the lipid-lowering effect [419].

Grade of recommendation — B;
level of evidence — 2.

Comments. In the multicenter comparative study RAKURS (262 patients), with the prophylactic administration of UDCA** simultaneously with HMG-CoA reductase inhibitors, no increase in serum transaminases was observed, but an increase in the hypolipidemic effect was noted [419, 420]. Liver diseases, including compensated cirrhosis, are not a limitation for the administration of HMG-CoA reductase inhibitors [421].

• In patients receiving methotrexate therapy**, **it is recommended** to prescribe folic acid** to prevent adverse reactions, including DILI [422, 423].

Grade of recommendation — A;
level of evidence — 1.

Comments. A number of side effects, including hepatotoxicity, associated with methotrexate** therapy are due to folic acid deficiency. According to a meta-analysis of RCTs, folic acid** prevents methotrexate-induced increase in serum transaminases** with a relative risk reduction of 76.9 % (absolute risk reduction of 16 %) and also reduces frequency of patient refusal to take methotrexate** for any reason (relative risk reduction of 60.8 %, absolute risk reduction of 15.2 %) [423]. Folic acid is administered at a dose of 5 mg/week on a different day than methotrexate**.

6. Organization of medical care

The current Federal Law No. 61-FL "On the circulation of medicinal product" dated April 12,

2010 (with subsequent amendments and additions) states that "medications in circulation in the Russian Federation are subject to efficacy and safety monitoring in order to identify possible negative consequences of their use, individual intolerance, warning healthcare workers… and their protection from the use of such medicinal products". Subjects of medicinal product circulation are obliged to report in the established manner "side effects, adverse reactions, serious adverse reactions, unexpected adverse reactions during the use of medicinal products, individual intolerance, lack of effectiveness of medicinal products, as well as other facts and circumstances posing a threat to the life or health of humans or animals during the use of medicinal products and identified at all stages of circulation of medicinal products in the Russian Federation and other countries" (Article 64. Pharmacovigilance) [424].

Medical care, with the exception of medical care within the framework of clinical trials, in accordance with the Federal Law of 21.11.2011 No. 323-FL "On the fundamentals of health protection of citizens in the Russian Federation", is organized and provided [425]:

Health care, with the exception of medical care within the framework of clinical trials, in accordance with Federal Law No. 323-FL of November 21, 2011, "On the fundamentals of health protection of citizens in the Russian Federation", is organized and provided:

1) in accordance with the regulations on the organization of medical care by type, which are approved by the authorized federal executive body;

2) in accordance with the procedures for providing care in the specialty of "gastroenterology", which are mandatory for implementation by all medical organizations in the Russian Federation [426];

3) on the basis of these clinical guidelines;

4) taking into account the standards of medical care approved by the authorized federal executive body.

The outpatient phase is for the management of patients with mild DILI, who have no risk factors for an unfavorable prognosis; patients with resolving DILI; and patients with chronic DILI.

The inpatient phase is for the management of patients with moderate to severe DILI and acute liver failure.

Indications for hospitalization

6.1. Indications for emergency hospitalization in a medical facility:

Moderate and severe DILI (including cases corresponding to Hay's law, with signs of acute liver failure).

6.2. Indications for planned hospitalization in a medical organization:

– the need for diagnostic procedures that cannot be performed on an outpatient basis (e.g., ultrasound-guided percutaneous liver biopsy or laparoscopic liver biopsy);

– the need for differential diagnostic procedures to exclude other causes of liver injury that cannot be performed on an outpatient basis (e.g., ultrasound-guided percutaneous liver biopsy or laparoscopic liver biopsy);

– the combination of DILI with other conditions that complicate its course, requiring multidisciplinary patient management and/or 24-hour monitoring.

In case of planned hospitalization, which is indicated for the performance of surgical diagnostic or therapeutic procedures (for example, performing an ultrasound-guided percutaneous liver biopsy or a laparoscopic liver biopsy), hospitalization is performed in a surgical hospital.

6.3. Indications for patient discharge from a medical facility:

– a sustained reduction in clinical and laboratory signs of the disease;

– compensation of developed complications, if they were observed previously;

– the absence of severe adverse reactions to the adjusted treatment;

– the possibility of oral administration of the drug and the elimination of the need for regular parenteral administration.

7. Additional information (including factors influencing the outcome of the disease or condition)

No additional information is available.

Criteria for assessing the quality of medical care

No.	Quality criteria	Performance assessment(yes/no)
1	An initial appointment (examination, consultation) with a gastroenterologist or general practitioner has been completed	Yes/No
2	The patient's drug history was assessed	Yes/No
3	A CBC test, a general biochemical blood test (with detection of the activity of ALT, AST, ALP, GGT, TBL, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, albumin, assessment of prothrombin (thromboplastin) time in the blood or plasma, determination of INR) were performed	Yes/No
4	The laboratory pattern of DILI was determined with the calculation of the *R* index	Yes/No
5	The assessment of compliance with the DILI criteria has been completed	Yes/No
6	The suspected drug, herbal product, or dietary supplement has been discontinued, except in cases where the drug is vital and there is no adequate alternative (if there are indications and no contraindications)	Yes/No
7	Treatment with acetylcysteine** was performed (in patients with paracetamol-induced DILI**)	Yes/No
8	Treatment with #levocarnitine was performed (in patients with valproic acid-induced DILI**)	Yes/No
9	Treatment with prednisolone** was performed (for patients with drug-induced autoimmune-like hepatitis)	Yes/No
10	An appointment for a follow-up observation (examination, consultation) with a gastroenterologist or general practitioner (family physician) or general physicians was made	Yes/No

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Appendix A2

Methodology for developing clinical guidelines

The purpose of the proposed recommendations is to convey to practicing physicians modern ideas about the etiology and pathogenesis of DILI, to introduce them to the currently used algorithms for diagnosis, prognosis assessment and treatment.

Target audience of these clinical guidelines:

1. Gastroenterologists.
2. General practitioners (family physicians).
3. General physicians.
4. Oncologists.

Table 1. Level of evidence (LoE) rating scale for diagnostic methods (diagnostic interventions)

LoE	Explanation
1	Systematic reviews of reference-controlled studies or systematic reviews of randomized clinical trials using meta-analysis
2	Individual reference-controlled studies or individual randomized clinical trials and systematic reviews of studies of any design except randomized clinical trials using meta-analysis
3	Studies without consistent control by a reference method or studies with a reference method that is not independent of the method explored, or non-randomized comparative studies, including cohort studies
4	Non-comparative studies, case report
5	Only action mechanism validation or expert opinion is available

Table 2. Levels of evidence (LoE) rating scale for methods of prevention, treatment, and medical rehabilitation, including those based on the use of natural healing factors (preventive, therapeutic, and rehabilitation interventions)

LoE	Explanation
1	Systematic reviews of reference-controlled studies or systematic reviews of randomized clinical trials using meta-analysis
2	Individual reference-controlled studies or individual randomized clinical trials and systematic reviews of studies of any design except randomized clinical trials using meta-analysis
3	Studies without consistent control by a reference method or studies with a reference method that is not independent of the method explored, or non-randomized comparative studies, including cohort studies
4	Non-comparative studies, case report
5	Only action mechanism validation or expert opinion is available

Table 3. Grades of recommendation (GR) rating scale for methods of prevention, diagnosis, treatment and medical rehabilitation, including those based on the use of natural healing factors (preventive, diagnostic, therapeutic and rehabilitation interventions)

GR	Explanation
A	Strong recommendation (all efficacy endpoints (outcomes) considered are important, all studies are of high or satisfactory methodological quality, and their conclusions on the outcomes of interest are consistent)
B	Conditional recommendation (not all efficacy endpoints (outcomes) considered are important, not all studies are of high or satisfactory methodological quality and/or their conclusions on the outcomes of interest are not consistent)
C	Weak recommendation (lack of evidence of adequate quality, all efficacy endpoints (outcomes) considered are unimportant, all studies are of low methodological quality and their conclusions on the outcomes of interest are not consistent)

Procedure for updating clinical guidelines

The mechanism of updating clinical guidelines provides for their systematic updating at least once every three years, as soon as new evidence-based data appears on diagnosis, treatment, prevention and rehabilitation of specific diseases, and upon availability of justified additions/comments to previously approved clinical guidelines, but no more than semi-annually.

Appendix A3

Reference materials, including compliance of indications for use and contraindications, methods of administration and dosages of drugs, instructions for use of the drug

These clinical guidelines were developed taking into account the following regulatory documents:

1. Order of the Ministry of Health of Russian Federation dated February 28, 2019 No. 103n "On approval of the procedure and deadlines for the development of clinical guidelines, their revision, the standard form of clinical guidelines and requirements for their structure, composition and scientific validity of the information included in clinical guidelines" (registered with the Ministry of Justice of Russian Federation on May 8, 2019 No. 54588).

2. Order of the Ministry of Health and Social Development of the Russian Federation dated November 12, 2012, No. 906n "On approval of the procedure for providing medical care to the population in the field of "Gastroenterology"" (registered with the Ministry of Justice of Russia on January 21, 2013, No. 2664).

3. Order of the Ministry of Health of the Russian Federation dated December 28, 2022 No. 810n "On approval of the standard of medical care for adults with liver cirrhosis and fibrosis (diagnosis and treatment)".

4. Order of the Ministry of Health of the Russian Federation dated May 10, 2017, No. 203n "On approval of criteria for assessing the quality of medical care".

Table 4. Main risk factors for the development of DILI [10]

Factor	The importance of the factor for the development of DIPP
Age	Determines susceptibility to DILI secondary to specific drugs and the DILI phenotype (for example, older age is a risk factor for DILI associated with isoniazid**, younger age associated with valproic acid** and NSAIDs)
Female gender	Higher risk of DILI with ALF, hepatocellular pattern of DILI
Ethnicity	Determines susceptibility to DILI, secondary to individual drugs
Excessive regular alcohol consumption	Increases the risk of DILI associated with certain drugs (isoniazid**, halothane**, paracetamol**, duloxetine, valproic acid**, anabolic steroids)
Components of metabolic syndrome (NAFLD, diabetes mellitus)	Increases the risk of tamoxifen-associated DILI**
Chronic hepatitis B and C	Increases the risk of DILI associated with antiretroviral and antituberculosis therapy

Table 5. Expert opinion scoring categories in assesment of causality in DILI (AASLD, 2023) [2]

Causality score	Likelihood (%)	Description
Definite	>95	Beyond any reasonable doubt
Highly likely	75–95	Clear and convincing data, but not definite
Probable	50–74	Most data support causal relationship
Possible	25–49	Most data suggest no causal relationship, but possibility remains
Unlikely	Менее 25	Causal relationship very unlikely, with alternative etiology more likely
Insufficient data	Determinable	Missing key data

Table 6. Some antitumor drugs and recommendations for dose modification in the event of hepatotoxicity

Medication	Pharmacological class of the drug, application	Warnings	Elevated liver panel values	Dose modification
Selpercatinib	Protein kinase inhibitors / various solid tumors (lung, thyroid)	Hepatotoxicity: ALT and AST levels must be monitored before starting therapy and every 2 weeks during the first 3 months of treatment, then once every month.	Serious liver AE occurred in 2.6 % of cases. ALT increased to G3–4 in 9 % of cases. AST increased to G3–4 in 8 % of cases. Bilirubin increased to G3–4 in 2 % of cases.	AST or ALT level G3–4: withhold the dose to G1 or baseline. Reduce the dose by 2 dose levels and monitor ALT/AST weekly. Increase the dose by 1 dose level after at least 2 weeks.
Capmatinib	Protein kinase inhibitors/metastatic non-small cell lung cancer	Hepatotoxicity: ALT and AST levels must be monitored before starting therapy and every 2 weeks during the first 3 months of treatment, then once every month.	Increase in ALT level to G3–4 = 8 %, increase in AST level to G3–4 = 4.9 %	AST or ALT level G3 without increase in bilirubin: cease the drug until the baseline transaminase level is restored.
Entrectinib	Protein kinase inhibitors/advanced non-small cell lung cancer	Hepatotoxicity: ALT and AST levels must be monitored before starting therapy and every 2 weeks during the first 3 months of treatment, then once every month.	Increase in ALT level to G3–4 = 2.9 %, increase in AST level to G3–4 = 2.7 %	ALT or AST levels G3–4: withhold the drug until transaminase levels return to G1 or baseline; resume at the same dose if the G3 event resolves within 4 weeks; or resume at a reduced dose if there are repeated increases to G3 or increases to G4. If ALT/AST levels rise to G4 repeatedly and Hay's law criteria are met, discontinue the drug without resuming
Polatuzumab vedotin **	Other monoclonal antibodies (CD79b-targeted antibody-drug conjugate/diffuse large B-cell lymphoma)	Hepatotoxicity: monitoring of transaminase and bilirubin levels is necessary.	In combination with R-CHP, elevated transaminase levels were observed in 10.6 % of cases, primarily in G1–2 and less frequently in G3. No G4–5 elevations were observed. In combination with R-CHOP, elevated transaminase levels were observed in 7.3 % of cases.	The drug should not be administered if the bilirubin level is > 1.5 ULN. No dose adjustment is required if the bilirubin level is < 1.5 ULN and the AST level is elevated.
Larotrectinib	Protein kinase inhibitors/NTRK gene fusion solid tumors without resistance mutation, metastatic without the possibility of surgical resection, without satisfactory alternative treatments	Hepatotoxicity: ALT and AST levels must be monitored every 2 weeks during the first month of treatment, then once a month and as indicated.	An increase in ALT and AST at level G1 is observed in 18 and 19 % of cases, respectively, at level G2 — 5 % of cases, and at level G3–4 — up to 3 % of cases.	The initial dose should be reduced by 50 % in patients with Child — Pugh cirrhosis B and C. The drug should be withheld and the dosage adjusted based on laboratory monitoring or permanently discontinued depending on the severity of hepatotoxicity.

Table endings 6. Некоторые противоопухолевые препараты и рекомендации по модификации доз при развитии гепатотоксичности

Medication	Pharmacological class of the drug, application	Warnings	Elevated liver panel values	Dose modification
Binimetinib	Protein kinase inhibitors/in combination with a B-Raf serine-threonine kinase inhibitor (BRAF), unresectable or metastatic melanoma with BRAF V600E or V600K mutations	Hepatotoxicity: Monitoring of liver panel parameters is necessary before, during treatment and when indicated.	In combination with encorafenib, ALT increased to G3–4 in 6 % of cases, AST to G3–4 in 2.6 %. ALP to G3–4 in 0.5 % of cases.	In combination with encorafenib, ALT increased to G3–4 in 6 % of cases, AST to G3–4 in 2.6 %. ALP to G3–4 in 0.5 % of cases. No adjustment of therapy is required for G2 ALT and AST elevations; if no improvement occurs within 2 weeks, discontinue treatment until improvement to G0–1 or to pre-treatment/baseline levels, then resume at the same dose. G3–4 AST or ALT elevations: at first G3–4 event (or G2 relapse), suspend treatment for ≤ 4 weeks; if transaminase levels decrease to G0–1 or to pre-treatment/baseline levels, resume at the same dose; if no improvement occurs, discontinue the drug. If recurrent events occur, consider permanent withdrawal of treatment. For patients with moderate or severe hepatic impairment, the recommended dose is 30 mg twice daily.
Abemaciclib**	Abemaciclib** Protein kinase inhibitors / advanced or metastatic breast cancer (HR^+, HER^-)	Hepatotoxicity: ALT, AST and total bilirubin levels must be monitored before starting therapy, every 2 weeks for the first 2 months, monthly for the next 2 months and then as clinically indicated.	Increased ALT and AST levels to G3–4 when used in combination with fulvestrant were observed in 6.1 and 4.2 % of cases, respectively.	If ALT and AST increase to G1–2, no dose adjustment is required. If ALT and AST increase to G3, discontinue the drug until transaminase levels return to G0–1 or to pre-treatment/baseline levels, then resume at a dose reduced to the previous level. If ALT and AST increase to G4 or Hay's law criteria are met, discontinue the drug without resuming treatment.

Note: *AE — adverse reactions; ULN — upper limit of normal.*

Table 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

Efficacy of #acetylcysteine in the treatment of DILI** [206, 207, 427–433]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	Drug (cause of DILI) for which there is insufficient data
1	Analgesics and antipyretics (N02B)	Paracetamol** (1 CCT [Keays, 1991], 4 SR [Chiew, 2018, Stine, 2016, Licata, 2022, Buckley, 2007])	
2	Antifungals for systemic use (J02)		Ketoconazole (1 SR [Niu, 2022])
3	Antineoplastic drugs (L01)		Cyclophosphamide**, busulfan**, fludarabine** 1 (1 RCT [Barkholt, 2008]), mercaptopurine** (1 RCT [vanAsseldonk, 2024])
4	Immunosuppressants (L04)		Antithymocyte immunoglobulin** (1 RCT [Barkholt, 2008]); azathioprine**
5	Drugs for the treatment of heart disease (C01)		Amiodarone** (1 SR [Jaiswal, 2018])
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; RCT — randomized clinical trial; SR — systematic review; 1 — in combination with radiation therapy; allogeneic hematopoietic stem cell transplantation.			
Efficacy of #acetylcysteine in the prevention of DILI** [411, 434–437]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, pyrazinamide**, ethambutol** (2 RCTs [Baniasadi, 2010, Farazi, 2015]; 1 MA [Singh, 2020]); anti-tuberculosis drugs (2 RCTs [Ahmed, 2020, Sukumaran, 2023])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; RCT — randomized clinical trial; MA — meta-analysis.			
Efficacy of #levocarnitine in the treatment of DILI [218, 438]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Antiepileptic drugs (N03)	Valproic acid** (1 RCT [Tincu, 2016], 1 SR [Perrott, 2010])	–
Notes: DLI — drug-induced liver injury; RCT — randomized clinical trial; SR — systematic review.			
Efficacy of #levocarnitine in the prevention of DILI [439]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, pyrazinamide**, ethambutol** (1 RCT [Hatamkhani, 2014])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; RCT — randomized clinical trial.			
Efficacy of UDCA in the treatment of DILI** [224, 227, 229, 231, 430, 440–443]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	Drug (cause of DILI) for which there is insufficient data
1	Systemic antimicrobials (J)	Ceftriaxone** (1 CCT [Ovcharenko 2013]); azithromycin** [Stepanov, 2021]; anti-tuberculosis drugs (1 RCT [Borzakova, 2012, Borzakova, 2016]); amoxicillin + clavulanic acid**, rifampicin**, isoniazid**, pyrazinamide** [Bessone, 2024]	Amoxicillin + clavulanic acid** (2 SR [Niu, 2022, Robles-Díaz, 2022]); Co-trimoxazole [sulfamethoxazole + trimethoprim]** (1 SR [Niu, 2022])
2	Systemic antimicrobials (J02)		Terbinafine (1 SR [Robles-Díaz, 2022])

Continuation of the Table 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

3	Antineoplastic drugs (L01)		Pembrolizumab**, brentuximabvedotin** (1 SR [Robles-Díaz, 2022])
4	Systemic hormonal drugs, except sex hormones and insulins (H), sex hormones and modulators of sexual function (G03), anabolic steroids (A14A)		Testosterone**, nandrolone**, thiamazole**, flutamide** (1 SR [Robles-Díaz, 2022])
5	Antihypertensive agents (C02)		Bosentan** (1 SR [Robles-Díaz, 2022])
6	Drugs affecting the nervous system (N)		Haloperidol**, amitriptyline**, phenytoin**, sertraline** (1 SR [Robles-Díaz, 2022])
7	Nonsteroidal anti-inflammatory and antirheumatic drugs (M01A)		Naproxen (1 SR [Robles-Díaz, 2022])
8	Immunosuppressants (L04)	Methotrexate** (1 RCT [Maksimova, 2015])	–
9	Bisphosphonates (M05BA)		bandronic acid (1 SR [Robles-Díaz, 2022])
Notes: MP – medicinal product; DILI – drug-induced liver injury; NSAIDs – non-steroidal anti-inflammatory and antirheumatic drugs; RCT – randomized clinical trial; SR – systematic review.			
Efficacy of UDCA in the prevention of DILI** [444–447]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	Drug (cause of DILI) for which there is insufficient data
1	Systemic antimicrobials (J)	Amoxicillin**, clarithromycin** (1 RCT [Andreev, 2020])	
2	Antineoplastic agents (L01); systemic corticosteroids (H02A)	Vincristine**, daunorubicin**, asparaginase**, cyclophosphamide**, cytarabine**, mercaptopurine**, methotrexate**, etoposide**, imatinib**, methylprednisolone**, dexamethasone** (1 RCT [MohammedSaif, 2012]); prednisolone**, doxorubicin**, vincristine**, asparaginase**, methotrexate** (1 RCT [Skripnik, 2020]);	Mercaptopurine** (2 RCTs [MohammedSaif, 2012, Bordbar, 2018]); prednisolone** (1 RCT [Skripnik, 2020], 2 RCTs [Bordbar, 2018])
3	Antiepileptic drugs (N03)	Valproic acid** (1 RCT [Shahramanian, 2020])	–
4	Proton pump inhibitors (A02BC); systemic anti-acne drugs (D10B)	Esomeprazole** (1 RCT [Andreev, 2020]); isotretinoin (1 RCT [Ledentsova, 2020])	–
Notes: MP – medicinal product; DILI – drug-induced liver injury; RCT – randomized clinical trial; SR – systematic review.			
Efficacy of ademetionine in the treatment of DILI** [239, 241, 245, 247, 248, 448–451]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, pyrazinamide**, ethambutol**, streptomycin**, prothionamide**, cycloserine**, aminosalicylic acid**, levofloxacin**, ciprofloxacin**, kanamycin**, amikacin**, rifabutin** (1 CCT [Sukhanov, 2012, Sukhanov, 2013a, Sukhanov, 2013b]); anti-tuberculosis drugs (1 RCT [Sukhanov, 2013c])	–

Continuation of the Table 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

2	Antineoplastic drugs (L01)	Doxorubicin**, cyclophosphamide**, fluorouracil**, vincristine**, paclitaxel**, carboplatin**, etoposide**, methotrexate**, cisplatin**, cytarabine**, procarbazine**, rituximab**, bortezomib** (1 SR [Noureddin, 2020]; 1 OP [Snegovoy, 2015]); unspecified (1 CCT [Klyaritskaya, 2013]); oxaliplatin**, irinotecan**, fluorouracil**, cyclophosphamide**, methotrexate** (1 NCT [Santini, 2003])	–
3	Immunosuppressants (L04); systemic corticosteroids (H02A)	Cyclosporine**, leflunomide**, betamethasone**, dexamethasone** (1 NCT [Noureddin, 2020]); methotrexate**, systemic corticosteroids (1 NCT [Perlamutrov, 2014])	–
4	Systemic hormonal drugs, except sex hormones and insulins (H), sex hormones and modulators of sexual function (G03), anabolic steroids (A14A)	Unspecified (1 CCT [Klyaritskaya, 2013])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; NCT — non-randomized clinical trial; RCT — randomized clinical trial; SR — systematic review; OP — observational program.			
Efficacy of #ademetionine in the prevention of DILI** [242, 265, 395, 409, 410, 452, 453]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	Drug (cause of DILI) for which there is insufficient data
1	Antineoplastic drugs (L01)	Cytarabine**, anthracyclines and related compounds, etoposide** (1 CCT [Skripnik, 2019]); fludarabine**, cyclophosphamide**, rituximab**, bendamustine**, vincristine**, prednisolone** (1 CCT [Skripnik, 2020]); bevacizumab**, oxaliplatin**, capecitabine**, fluorouracil** (NCT [Vincenzi, 2011, 2012, 2018])	Bevacizumab**, oxaliplatin** (1 SR [Benić, 2022])
2	Immunosuppressants (L04)	Methotrexate** (1 CCT [Ugryumova, 2010])	–
Notes: DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial.			
Efficacy of phospholipids in the treatment of DILI [253, 254, 410, 454]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Anti-tuberculosis drugs (1 CCT [Liu, 2021]; 1 MA [Li, 2023])	–
2	Кортикостероиды системного действия (H02A)	Methylprednisolone** (1 CCT [Palgova, 2017])	–
3	Sex hormones and modulators of sexual function (G03)	Progestogens, estrogens, human chorionic gonadotropin** (1 CCT [Palgova, 2017])	–
4	Antiepileptic drugs (N03)	Phenytoin**, phenobarbital** (1 CCT [Hisanaga, 1980])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; MA — meta-analysis.			
Efficacy of ornithine in the treatment of DILI [261, 262, 265, 452, 455–459]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–

Continuation of the Table 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

1	Antineoplastic drugs (L01)	Cyclophosphamide**, bortezomib**, dexamethasone** (1 RCT [Skrypnik, 2018]); antimetabolites, platinum compounds, alkylating agents, anthracyclines and related compounds, taxanes, plant-based alkaloids and other natural substances (1 RCT [Scheller, 1998]); unspecified (2 NCCTs [Larionova, 2009, Maksimova, 2018], 1 CNCT [Soldatova, 2022]); platinum compounds, taxanes, anthracyclines and related compounds (1 RCT [Matsishevskaya, 2011]); cyclophosphamide**, bortezomib** (1 CNCT [Skrypnik, 2018])	–
2	Drugs affecting the nervous system (N)	Clozapine (1 CCT [Slyundin, 2010]); psycholeptics (1 CCT [Ostapenko, 2006])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; RCT — randomized clinical trial; CNCT — comparative non-randomized clinical trial; NCCT — non-comparative clinical trial.			
Efficacy of a fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid in the treatment of DILI** [247, 248, 277, 460–462]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, pyrazinamide**, ethambutol**, prothionamide**, cycloserine**, aminosalicylic acid**, levofloxacin**, ciprofloxacin**, kanamycin**, amikacin**, rifabutin** (1 CCT [Sukhanov, 2013a]); anti-tuberculosis drugs (2 RCTs [Sukhanov, 2013b], 2 CCTs [Sukhanov, 2009, Shevyreva, 2012]); systemic antibacterial drugs (1 CCT [Pavlov, 2025])	–
2	Antiviral agents for systemic use (J05)	Direct-acting antiviral drugs [for the treatment of HIV infection] (1 CCT [Shevyreva, 2012])	–
3	Antineoplastic drugs (L01)	Docetaxel**, cisplatin**, fluorouracil**1 (1 CCT [Ivanova, 2023])	–
4	Nonsteroidal anti-inflammatory and antirheumatic drugs (M01A)	NSAIDs (1 RCT [Pavlov, 2025])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; RCT — randomized clinical trial; NSAIDs — non-steroidal anti-inflammatory and antirheumatic drugs; 1 — in combination with radiation therapy.			
Efficacy of the fixed combination of inosine + meglumine + methionine + nicotinamide + succinic acid in the prevention of DILI** [270, 278, 282, 284, 381, 463, 464]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, rifabutin**, rifapentine, pyrazinamide**, ethambutol**, streptomycin**, kanamycin**, amikacin**, capreomycin**, levofloxacin**, moxifloxacin**, sparfloxacin**, prothionamide**, ethionamide**, bedaquiline**, linezolid**, cycloserine**, terizidone**, aminosalicylic acid**, delamanid** (1 RCT [Volchegorsky 2016]); anti-tuberculosis drugs (1 RCT [Kolomiets, 2019])	–

Continuation of the Table 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

2	Antineoplastic drugs (L01)	Fluorouracil**, doxorubicin**, cyclophosphamide** (1 CCT [Konopatskaya, 2015]); etoposide**, cisplatin**, cyclophosphamide**, doxorubicin** (1 CCT [Cherenkov, 2013]); cisplatin**, carboplatin**, doxorubicin**, cyclophosphamide** (1 RCT [Bondarenko, 2020]); FOLFOX/FLOX1, XELOX2, CF3, DCF4, XP5 (1 CCT [Drogomiretskaya, 2018]); FOLFOX1, FOLFIRI6 (calcium folinate**, fluorouracil**, irinotecan**) (1 CCT [Konopatskaya, 2016]); fluorouracil**, cisplatin**, methotrexate**7 (1 CCT [Matyakin, 2013]); unspecified (1 RCT [Tumanyan, 2022])	–
3	Drugs affecting the nervous system (N)	Sevoflurane**, ropivacaine**, lidocaine**, midazolam**, fentanyl**, nefopam (1 RCT [Tumanyan, 2022]); haloperidol**, trifluoperazine** (1 CCT [Filippova, 2019])	–
4	Nonsteroidal anti-inflammatory and antirheumatic drugs (M01A)	NSAIDs (1 RCT [Tumanyan, 2022])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial; RCT — randomized clinical trial; NSAIDs — non-steroidal anti-inflammatory and antirheumatic drugs; 1 — calcium folinate** + fluorouracil** + oxaliplatin**; 2 — capecitabine** + oxaliplatin; 3 — cisplatin** + fluorouracil**; 4 — docetaxel** + cisplatin** + fluorouracil**; 5 — capecitabine** + cisplatin**; 6 — calcium folinate** + fluorouracil** + irinotecan**; 7 — in combination with radiation therapy.			
Efficiency of #bicyclol in the treatment of DILI [290, 291, 293, 296]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Beta-lactam antibacterial drugs, penicillins (1 RCT [Tang, 2022], 1 CO [Niu, 2021]); anti-tuberculosis drugs (1 RCT [Tang, 2022], 1 SO [Niu, 2021])	–
2	Antineoplastic drugs (L01)	Unspecified (1 RCT [Tang, 2022])	–
3	Immunosuppressants (L04)	Unspecified (1 RCT [Tang, 2022])	–
4	Hormonal contraceptives for systemic use (G03A), anabolic steroids (A14A)	Systemic hormonal contraceptives, anabolic steroids (1 RCT [Tang, 2022])	–
5	Lipid-lowering agents (C10)	Atorvastatin**, simvastatin** (1 RCT [Naiqiong, 2017], 1 SR [Niu, 2021]);	–
6	Drugs affecting the nervous system (N)	Unspecified (1 RCT [Tang, 2022])	–
Notes: MP — medicinal product; DILI — drug-induced liver injury; RCT — randomized clinical trial; SR — systematic review.			
Efficacy of #bicyclol in the prevention of DILI [290, 292, 294]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	–
1	Systemic antimicrobials (J)	Isoniazid**, rifampicin**, pyrazinamide**, ethambutol** (1 RCT [Chu, 2015], 1 SR [Niu, 2021])	–
2	Antineoplastic drugs (L01)	FOLFOX[1], XELOX[2], CHOP[3], docetaxel**, paclitaxel**, gemcitabine**, irinotecan**, etoposide** (1 RCT [Li, 2014], 1 SR [Niu, 2021])	–
3	Systemic corticosteroids (H02A)	Prednisolone** (1 RCT [Li, 2014], 1 SR [Niu, 2021])	–

Table endings 7. Efficacy of hepatotropic drugs (A05, drugs for the treatment of liver and biliary tract diseases) in the treatment and prevention of DILI

Notes: MP — medicinal product; DILI — drug-induced liver injury; RCT — randomized clinical trial; SR — systematic review; [1] — calcium folinate**, fluorouracil**, oxaliplatin**; [2] — capecitabine**, oxaliplatin**; [3] — cyclophosphamide**, doxorubicin**, vincristine**, prednisolone**.			
Efficacy of morpholinium thiazotate in the treatment of DILI [304]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	—
1	Systemic antimicrobials (J)	Anti-tuberculosis drugs (1 NCT [Shovkun, 2013])	—
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial.			
Efficacy of morpholinium thiazotate in the prevention of DILI [303–305, 465]			
No.	Etiology of DILI (drug group)	MP (cause of DILI) for which a positive effect has been shown	—
1	Systemic antimicrobials (J)	Systemic antibacterial drugs (1 RCT [Grechkanev, 2012]); anti-tuberculosis drugs (1 RCT [Shovkun, 2025]; 1 RCT [Shovkun, 2013])	—
2	Antineoplastic drugs (L01)	Doxorubicin**, cyclophosphamide**, vincristine**, rituximab** (1 CCT [Koltsov, 2023])	—
3	Systemic antihistamines (R06)	Systemic antihistamines (1 CCT [Grechkanev, 2012])	—
4	Antithrombotic agents (B01)	Antiplatelet agents other than heparin (1 CCT [Grechkanev, 2012])	—
Notes: MP — medicinal product; DILI — drug-induced liver injury; CCT — non-randomized controlled clinical trial.			

Table 8. King's College Hospital criteria for DILI [182]

Paracetamol** induced ALF	Non-paracetamol** acute liver failure
Arterial pH < 7.3 or	INR > 6.5 or
3 criteria out of 3: — INR > 6.5; — serum creatinine > 300 umol/L; — hepatic encephalopathy (Grades III or IV)	3 criteria out of 5: — age of less than 11 or greater than 40; — serum bilirubin > 300 umol/L; — time from onset of jaundice to the development of coma > 7 days — drug toxicity, regardless of whether it was the cause of the acute liver failure

Prognostic models

1. Acute liver failure study group (ALFSG) prognostic model for predicting 21-day transplant-free survival (TFS) in patients with ALF [180]

Logit TFS = 2.67 — 0.95 (HE) + 1.56 (Etiology) — 1.25 (Vasopressor Use) — 0.70 (ln bilirubin) — 1.35 (ln INR),
where: hepatic encephalopathy (HE) stage 1–2 = 0, stage 3–4 = 1, etiology: 1 = known (paracetamol**/pregnancy/ischemia/HAV), 0 = other.
Logit TFS can be transformed into the predicted probability of TFS with the following formula:
Predicted TFS = 1/(1 + e(—1*Logit TFS)).
A prognosis of > 20 % probability of TFS is an indication for inclusion on the LT waitlist.

2. MELD (Model for End-Stage Liver Disease) prognostic model

MELD = (0.957 × ln(serum creatinine, mg/dL × 88.4[1]) + 0.378 × ln(serum bilirubin, mg/dL × 117.104[2]) + 1.120 × ln(INR) + 0.643) × 10 (if creatinine is 4.0 mg/dL during hemodialysis at least twice in the last 7 days),

where: ln — natural logarithm; INR — international normalized ratio; 1 — the creatinine conversion factor from mg/dL to umol/L; 2 — the bilirubin conversion factor from mg/dL to umol/L.

Values < 1 mg/dL (<88.4 umol/L creatinine and <17.104 umol/L bilirubin) are considered equal to 1.

Interpretation: For DILI, an unfavorable prognosis is associated with a MELD value of > 19.

Liver Transplant Urgency (according to UNOS criteria)

Status 1: Acute liver failure in adults, acute or chronic failure in children (under 18 years) with an expected survival without liver transplantation of less than 7 days in the intensive care unit (ICU). Stage 2A: Chronic liver disease with an expected survival without liver transplantation of less than 7 days in the ICU.

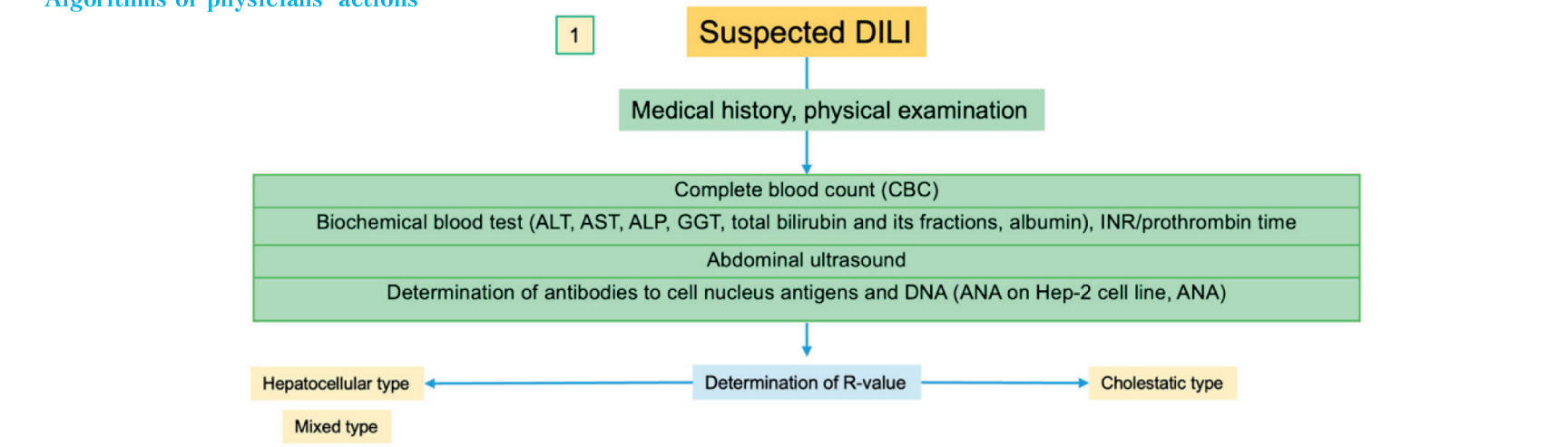
Stage 2B: ICU stay of at least 5 days due to acute liver failure.

Stage 3: Requirement for permanent hospitalization.

Table 9. Determination of the urgency status of patients on the liver transplant waiting list (according to UNOS)

Status 1	Acute liver failure	Patients with acute liver failure, or patients with primary graft dysfunction or hepatic artery thrombosis that developed in the first weeks after transplantation, or children with decompensated cirrhosis requiring permanent stay in the intensive care unit
Status 2A	Decompensated liver disease and life expectancy less than 7 days	hild — Turcotte — Pugh (CTP) score ≥ 10, intensive care unit admission, and life expectancy less than 7 days
Status 2B	Decompensated chronic liver disease	CTP score 7–10 in combination with refractory complications of portal hypertension syndrome or the presence of hepatocellular carcinoma with the following parameters: 1 lesion up to 5 cm or ≤ 3 foci up to 3 cm each in the absence of signs of metastasis
Status 3	Stable chronic liver disease	CTP score ≥ 7

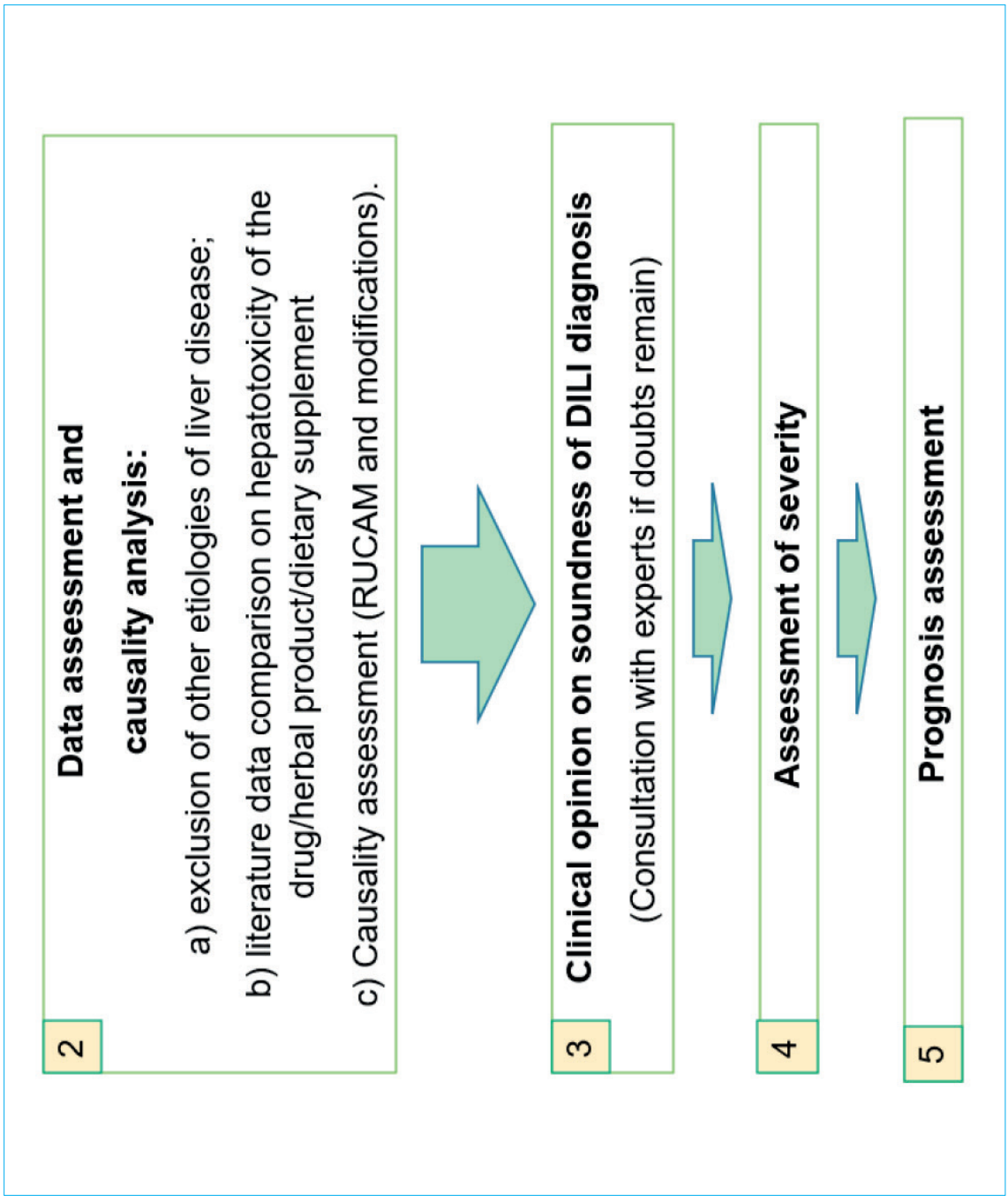
Appendix B.
Algorithms of physicians' actions



1-st line workup
Determination of class M antibodies (anti-HAV IgM) to the hepatitis A virus (Hepatitis A virus), antigen (HbsAg) of hepatitis B virus (Hepatitis B virus), total antibodies of classes M and G (anti-HCV IgG and anti-HCV IgM) to hepatitis C virus (Hepatitis C virus) in blood
Determination of immunoglobulin G levels in blood, anti-smooth muscle antibodies (ASMA), antibodies to cell nucleus antigens and DNA (ANA on Hep-2 cell line, ANA) in blood
Determination of creatine kinase activity in blood (when AST > ALT)
2-nd line workup (for specific patients)
Determination of thyroid-stimulating hormone (TSH) levels, antibodies to tissue transglutaminase in the blood (IgA)
Hepatitis C virus RNA in blood using PCR, qualitative testing, anti-HEV IgM and anti-HEV IgG antibodies to hepatitis E virus in blood, Hepatitis E virus RNA in feces using PCR
Determination of class M (IgM) and class G (IgG) antibodies to herpes simplex virus types 1 and 2 (Herpes simplex virus types 1, 2) in blood, class M (IgM) and G (IgG) antibodies to varicella-zoster virus in blood, class M, G (IgM, IgG) antibodies to cytomegalovirus (Cytomegalovirus) in the blood, class M (IgM) and class G (IgG) antibodies to the capsid antigen (VCA) of Epstein-Barr virus (Epstein-Barr virus) in the blood, class G (IgG) antibodies to early proteins (EA) of the Epstein-Barr virus (Epstein-Barr virus) in the blood, classes M, G (IgM, IgG) antibodies to the Epstein-Barr virus (Epstein-Barr virus) in the blood
Transferrin iron saturation, ferritin levels, ceruloplasmin levels in blood, urine copper level (daily excretion)
Computed tomography of the abdominal organs and retroperitoneal space with intravenous bolus contrast, duplex scanning of the inferior vena cava and veins of the portal system
Liver biopsy under ultrasound guidance, pathological examination of biopsy (surgical) material from liver puncture biopsy

1-st line workup
Determination of antimitochondrial antibodies in blood (AMA)
Magnetic resonance cholangiopancreatography
2-nd line workup (for specific patients)
Endosonography of the pancreatobiliary zone
Liver biopsy under ultrasound guidance, pathological examination of biopsy (surgical) material from liver puncture biopsy

Figure 1. Algorithm of actions in case of suspected DILI



Continuation of the Figure 1. Algorithm of actions in case of suspected DILI

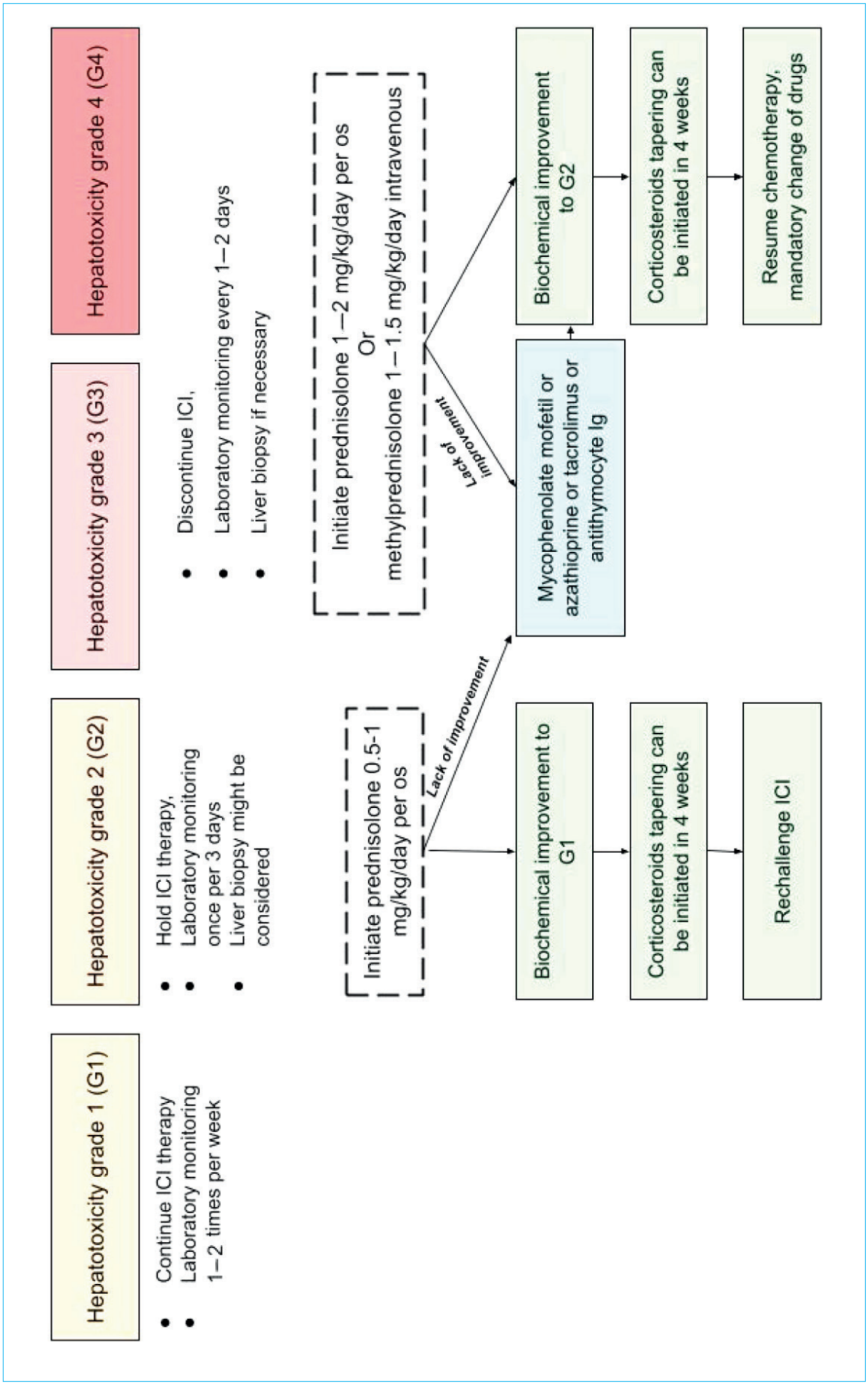


Figure 2. Approach to the treatment of hepatotoxicity associated with ICI (RUSSCO 2024 Practice Guidelines with amendments)

Appendix B

Information for the patient

If a patient needs or desires to take any medications, including herbal remedies and dietary supplements, they should consult a doctor. Self-administration of such medications and dietary supplements can be very dangerous. Independently reviewing the instructions for use of medications is often of no help to the patient, as these documents may contain incomplete information or be confusing to someone not trained in medicine.

It's also important to consult a doctor if you need to take multiple medications simultaneously, as this increases the risk of drug-induced liver injury. It's important to remember that taking large doses of paracetamol**, a commonly used antipyretic, can be potentially fatal due to acute liver failure.

Any symptoms that develop during or shortly after taking new medications or dietary supplements should be reported immediately. Particularly concerning are the following symptoms: yellowing of the sclera, abdominal pain/discomfort, nausea/vomiting, itching, light-colored stools and dark urine, fever, and severe weakness. Self-medication when symptoms appear is unacceptable and can be very dangerous.

Appendix D1–DN

Rating scales, questionnaires and other patient assessment instruments provided in clinical guidelines

Appendix D1

RUCAM scale for quantitative assessment of causality in cases of suspected DILI [147]

Title in Russian: –

Original title (if any):

CIOMS/RUCAM (Councils for International Organizations of Medical Science/Roussel Uclaf Causality Assessment Method)

Source:

1. *Danan G., Benichou C.* Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. J Clin Epidemiol. 1993;46(11):1323–30. DOI: 10.1016/0895-4356(93)90101-6
2. *Benichou C., Danan G., Flahault A.* Causality assessment of adverse reactions to drugs – II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol. 1993;46(11):1331–6. DOI: 10.1016/0895-4356(93)90102-7

Type (underline):

– rating
– index
– questionnaire
– other (specify)

Purpose: Used to quantify causality in cases of suspected DILI.

Contents (template): Considers clinical and biochemical data, assessment of the likelihood of other liver diseases, and a repeat drug challenge. It consists of two parts; the part corresponding to each laboratory pattern is filled out according to the *R* value.

A. Updated RUCAM for the hepatocellular injury

Items for hepatocellular injury	Score
1. Time to onset from the beginning of the drug/herb	
• 5–90 days (rechallenge: 1–15 days)	+2
• <5 or >90 days (rechallenge: >15 days)	+1
Alternative: Time to onset from cessation of the drug/herb	
• ≤15 days (except for slowly metabolized chemicals: >15 days)	+1
2. Course of ALT after cessation of the drug/herb	
Percentage difference between ALT peak and N	
• Decrease ≥ 50 % within 8 days	+3
• Decrease ≥ 50 % within 30 days	+2
• No information or continued drug use	0
• Decrease ≥ 50 % after day 30	0
• Decrease < 50 % after day 30 or recurrent increase	–2
3. Risk factors	
• Alcohol use (current drinks/day: >2 for women, >3 for men)	+1
• Alcohol use (current drinks/day: ≤2 for women, ≤3 for men)	0
• Age ≥ 55 years	+1
• Age < 55 years	0
4. Concomitant drug(s)/herb(s)	
• None or no information	0
• Concomitant drug/herb with incompatible time to onset	0
• Concomitant drug/herb with compatible or suggestive time to onset	–1
• Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset delete marking right side above	–2
• Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	–3
Group II (5 causes)	
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	
• Infection suggested by PCR and titer change for	
– CMV (anti-CMV-IgM, anti-CMV-IgG)	
– EBV (anti-EBV-IgM, anti-EBV-IgG)	
– HSV (anti-HSV-IgM, anti-HSV-IgG)	
– VZV (anti-VZV-IgM, anti-VZV-IgG)	
Evaluation of Groups I and II	
• All causes-groups I and II – reasonably ruled out	+2
• The 7 causes of Group I ruled out	+1
• 6 or 5 causes of Group I ruled out	0
• Less than 5 causes of Group I ruled out	–2
• Alternative cause highly probable	–3
6. Previous hepatotoxicity of the drug/herb	
• Reaction labelled in the product characteristics	+2
• Reaction published but unlabeled	+1
• Reaction unknown	0
7. Response to unintentional reexposure	
• Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	+3
• Doubling of ALT with the drug(s)/herb(s) already given at the time of first reaction	+1
• Increase of ALT but less than N in the same conditions as for the first administration	–2
• Other situations	0

B. Updated RUCAM for the cholestatic or mixed liver injury

Items for cholestatic or mixed liver injury	Score
1. Time to onset from the beginning of the drug/herb	
• 5–90 days (rechallenge: 1–90 days)	+2
• <5 or >90 days (rechallenge: > 90 days)	+1
Alternative: Time to onset from cessation of the drug/herb	
• (except for slowly metabolized chemicals: ≤30 days)	+1
2. Course of ALP after cessation of the drug/herb	
Percentage difference between ALP peak and N	
• Decrease ≥ 50 % within 180 days	+2
• Decrease < 50 % within 180 days	+1
• No information, persistence, increase, or continued drug/herb use	0
3. Risk factors	
• Alcohol use current drinks/day: >2 for women, >3 for men)	+1
• Alcohol use (current drinks/day: ≤2 for women, ≤3 for men)	0
• Pregnancy	+1
• Age ≥ 55 years	+1
• Age < 55 years	0
4. Concomitant use of drug(s)/herb(s)	
• None or no information	0
• Concomitant drug/herb with incompatible time to onset	0
• Concomitant drug/herb with compatible or suggestive time to onset	–1
• Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset	–2
• Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	–3
5. Search for alternative causes	
Group I (7 causes)	
• HAV: Anti-HAV-IgM	
• HBV: HBsAg, anti-HBc-IgM, HBV-DNA	
• HCV: Anti-HCV, HCV-RNA	
• HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	
• Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MRC	
• Alcoholism (AST/ALT ≥ 2)	
• Acute recent hypotension history (particularly if underlying heart disease)	
Group II (5 causes)	
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	
• Infection suggested by PCR and titer change for	
• CMV (anti-CMV-IgM, anti-CMV-IgG)	
• EBV (anti-EBV-IgM, anti-EBV-IgG)	
• HSV (anti-HSV-IgM, anti-HSV-IgG)	
• VZV (anti-VZV-IgM, anti-VZV-IgG)	
Evaluation of Group I and II	
• All causes — Groups I and II — reasonably ruled out	+2
• The 7 causes of Group I ruled out	+1
• 6 or 5 causes of Group I ruled out	0
• Less than 5 causes of Group I ruled out	–2
• Alternative cause highly probable	–3
6. Previous hepatotoxicity of the drug/herb	
• Reaction labelled in the product characteristics	+2
• Reaction published but unlabeled	+1
• Reaction unknown	0
7. Response to unintentional reexposure	
• Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure	+3
• Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction	+1
• Increase of ALP but less than N in the same conditions as for the first administration	–2
• Other situations	0

Key (interpretation):
≤0 points — DILI is excluded;
1–2 points — DILI is unlikely;
3–5 points — DILI is possible;
6–8 points — DILI is likely;
≥9 points — DILI is highly likely.

Appendix D2

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (November 2017) grades

Title in Russian: Критерии тяжести гепатотоксичности Национального института рака США (CTCAE), версия 5 (от ноября 2017 г.)

Original title (if any): Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, published November 2017.

Source: https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf

Type (underline):
– rating
– index
– questionnaire
– other (specify)

Purpose: to assess the severity of hepatotoxicity during anticancer therapy.

Content (template): criteria are based on the frequency of deviations from the upper limit of normal (ULN) or average baseline values of serum liver tests (ALT, AST, GGT, and ALP), as well as clinical and instrumental data.

Parameter	Grade			
	1	2	3	4
Alkaline phosphatase (ALP)	> ULN to 2.5 × ULN if baseline was normal; 2.0 to 2.5 × baseline if baseline was abnormal	>2.5 to 5.0 × ULN if baseline was normal; >2.5 to 5.0 × baseline if baseline was abnormal	>5.0 to 20 × ULN if baseline was normal; >5.0 to 20 × baseline if baseline was abnormal	>20 × ULN if baseline was normal; >20 × baseline if baseline was abnormal
Total bilirubin	> ULN to 1.5 × ULN if baseline was normal; >1 to 1.5 × baseline if baseline was abnormal	>1.5 to 3.0 × ULN if baseline was normal; >1.5 to 3.0 × baseline if baseline was abnormal	>3 to 10 × ULN if base.0line was normal; >3 to 10 × baseline if baseline was abnormal	>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal
GGT	> ULN to 2.5 × ULN if baseline was normal; 2.0 to 2.5 × baseline if baseline was abnormal	>2.5 to 5.0 × ULN if baseline was normal; >2.5 to 5.0 × baseline if baseline was abnormal	>5.0 to 20 × ULN if baseline was normal; >5.0 to 20 × baseline if baseline was abnormal	>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal
Aspartate aminotransferase	> ULN to 3.0 × ULN if baseline was normal; 1.5 to 3.0 × baseline if baseline was abnormal	>3.0 to 5.0 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal	>5.0 to 20 × ULN if baseline was normal; >5.0 to 20 × baseline if baseline was abnormal	>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal
Alanine aminotransferase	> ULN to 3.0 × ULN if baseline was normal; 1.5 to 3.0 × baseline if baseline was abnormal	>3.0 to 5.0 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal	>5.0 to 20 × ULN if baseline was normal; >5.0 to 20 × baseline if baseline was abnormal	>20 × ULN if baseline was normal; >20 × baseline if baseline was abnormal

Table endings. Grade

Parameter	Grade			
	1	2	3	4
Hepatic failure	no	no	Asterixis (flapping tremor); mild encephalopathy; limiting self-care activities of daily living	Severe encephalopathy; coma
Portal vein flow	normal	Decreased portal vein flow	Reversal/retrograde portal vein flow associated with esophageal varices / ascites	Life-threatening consequences; urgent intervention needed

Key (interpretation): the degree of hepatotoxicity is assigned based on the worst parameter.

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