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Clinical Practice Guidelines of the Russian Society for the Study of the Liver, the Russian Gastroenterological Association, the National Scientific Society of Infectious Disease Specialists for the Diagnosis and Treatment of Chronic Hepatitis C

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Aim: diagnosis and treatment algorithms in the clinical recommendations intended for general practitioners, gastroenterologists, infectious disease specialists, hepatologists on the of chronic hepatitis C are presented.

Summary. Chronic viral hepatitis C is a socially significant infection, the incidence of which in the Russian Federation remains significantly high. Over the past 10 years, great progress has been made in the treatment of hepatitis C — direct acting antiviral drugs have appeared. The spectrum of their effectiveness allows to achieve a sustained virological response in more than 90 % of cases, even in groups that were not previously considered even as candidates for therapy or were difficult to treat — patients receiving renal replacement therapy, after liver transplantation (or other organs), at the stage of decompensated liver cirrhosis, HIV co-infected, etc. Interferons are excluded from the recommendations due to their low effectiveness and a wide range of adverse events. The indications for the treatment have been expanded, namely, the fact of confirmation of viral replication. The terms of dispensary observation of patients without cirrhosis of the liver have been reduced (up to 12 weeks after the end of therapy). Also, these recommendations present approaches to active screening of hepatitis in risk groups, preventive and rehabilitation measures after the end of treatment.

Conclusion. Great success has been achieved in the treatment of chronic hepatitis C. In most cases, eradication of viral HCV infection is a real task even in patients at the stage of cirrhosis of the liver, with impaired renal function, HIV co-infection, after solid organs transplantation.

Keywords: hepatitis C, virus, HCV infection, liver cirrhosis, liver transplantation, co-infection, liver cancer, drugs with direct antiviral action, ribavirin

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Клинические рекомендации Российского общества по изучению печени, Российской гастроэнтерологической ассоциации, Национального научного общества инфекционистов по диагностике и лечению хронического вирусного гепатита С

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Цель исследования: в клинических рекомендациях, предназначенных для врачей-терапевтов, врачей общей практики, гастроэнтерологов, инфекционистов, представлены современные положения по диагностике и лечению хронического гепатита С.

Основное содержание. Хронический вирусный гепатит С — социально значимая инфекция, заболеваемость которой в Российской федерации остается высокой. За последние 10 лет достигнуты большие успехи в лечении гепатита С — появились препараты с прямым противовирусным действием. Спектр их эффективности позволяет достичь устойчивого вирусологического ответа более чем в 90 % случаев, даже в группах, которые ранее не рассматривались как кандидаты на терапию или были трудными для излечения: пациенты, получающие заместительную почечную терапию, после трансплантации печени и других органов, на стадии декомпенсированного цирроза печени, с коинфекцией ВИЧ и др. Из рекомендаций исключены препараты интерферонов ввиду их низкой эффективности и широкого спектра нежелательных явлений. Расширены показания к назначению лечения, а именно — факт подтверждения репликации вируса. Сокращены сроки диспансерного наблюдения пациентов без цирроза печени (до 12 недель после окончания терапии). Также в данных рекомендациях представлены подходы к активному скринингу гепатита в группах риска, профилактические и реабилитационные мероприятия после окончания лечения.

Заключение. Достигнуты большие успехи в лечении хронического вирусного гепатита С. В большинстве случаев эрадикация вирусной HCV-инфекции — реальная задача даже у пациентов на стадии цирроза печени, с нарушением функции почек, коинфекцией ВИЧ, после трансплантации печени и других органов.

Ключевые слова: гепатит С, вирус, HCV-инфекция, цирроз печени, трансплантация печени, коинфекция, рак печени, препараты с прямым противовирусным действием, рибавирин

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List of abbreviations

****** — indicated at the end of the name of the drug or combination of drugs, means their belonging to the list of VEDD
# — indicated at the beginning of the name of the medicinal product or the scheme of drugs used not according to the medical instructions (off-label)
Anti-HCV — antibodies to hepatitis C virus
Anti-HBc — antibodies to the nuclear antigen of the hepatitis B virus
HBcAg — hepatitis B core antigen, hepatitis B virus nuclear antigen
HBsAg — hepatitis B surface antigen, hepatitis B virus surface antigen
HBV — hepatitis B virus, hepatitis B virus
HCVcAg — hepatitis C virus core antigen, nuclear antigen of hepatitis C virus
HCV — hepatitis C virus
HIV — human immunogenicity virus, human immunodeficiency virus
MELD — model of the end-stage liver disease, calculated index, characteristic of the severity of end-stage liver disease
NS3/4A inhibitors — antiviral agents for the treatment of hepatitis C, block non-structural proteins NS3 and NS4A hepatitis C virus (J05AE protease inhibitors)
NS5A inhibitors — antiviral agents for the treatment of hepatitis C, block the non-structural protein NS5A of hepatitis C virus (J05AX other antiviral drugs)
ALT — alanine aminotransferase
AST — aspartate aminotransferase
AFP — Alpha-Fetoprotein
CHC — chronic hepatitis C
CKD — chronic kidney disease
DAAs — direct-acting antiviral drugs
DAK** — daclatasvir**
DSV; OBV+PTV/r** — dasabuvir; ombitasvir + paritaprevir + ritonavir**
DNA — deoxyribonucleic acid
EV — esophageal varices
GGT — gamma-glutamyltransferase
GLE+PIB** — glecaprevir + pibrentasvir**
GRA+ELB** — grazoprevir + elbasvir**
GT — genotype
GFR — glomerular filtration rate
HBV — hepatitis B virus
HCC — hepatocellular carcinoma
HCV — hepatitis C virus
HV — viral load
HIV — human immunodeficiency virus
IU — international unit
ICD 10 — International Classification of Diseases 10th Revision
LED+SOFA — ledipasvir + sofosbuvir
LC — liver cirrhosis
NRV** — narlaprevir**
NRV/r****— narlaprevir**, boosted with ritonavir**
OTP — orthotopic liver transplantation
PegIFN** — Peginterferon alfa-2a (40 kDa)** or Peginterferon alpha 2b**
PTI — prothrombin index
RBV** — ribavirin**
RNA — ribonucleic acid
SOFA** — sofosbuvir**
tab. — pill
Ultrasound — ultrasound examination
SVR — sustainable virological response
SVR12 — sustained virological response 12 weeks after the end of therapy
VEL+SOFA** — velpatasvir + sofosbuvir**

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

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

APRI (AST to Platelet count Ratio Index) is a non-commercial non-invasive calculated index of liver fibrosis, a method of non-invasive diagnosis. It can be used as an alternative in case of inaccessibility of liver transient elastometry.

Chronic hepatitis C (CHC) is a chronic inflammatory disease for more than 6 months with a predominant injury of the liver tissue due to infection with the hepatitis C virus (HCV — hepatitis C virus), which can lead to serious complications — liver cirrhosis (LC), liver cancer (hepatocellular carcinoma, HCC) and death.

Co-infection is infection with two or more infectious agents. In the case of chronic viral hepatitis C, it is usually used in combination with hepatitis B, D and HIV.

FIB-4 is a non-commercial non-invasive calculated index of liver fibrosis, a method of non-invasive diagnosis. It can be used as an alternative if liver transient elastometry is not available.

Genotypes of the hepatitis C virus — variants of the hepatitis C virus, are divided on the basis of differences in the nucleotide sequence of certain regions of the genome of the virus. In clinical practice, they are of great importance

for the choice of antivirals, if genotype-specific drugs are used.

Hepatitis is an inflammation in the liver tissue, characterized by the presence of necroinflammatory changes in the liver biopsy.

Hepatocellular carcinoma — a malignant tumor of the liver, is one of the possible outcomes of chronic viral hepatitis C, occurs as a rule in the cirrhotic liver.

Liver fibrosis — the process of replacing the parenchymal tissue of the liver with connective tissue, is a universal reaction of the body to chronic damage.

Liver cirrhosis — the terminal stage of chronic liver disease, characterized by the replacement of the parenchyma with connective tissue and a violation of the architecture of the organ. In the early stages, with preserved liver function, it is called compensated, with loss of function — decompensated.

METAVIR is a system for assessing the degree of inflammation (from A0 to A3) and fibrosis (from F0 to F4) in liver tissue. It is used both to characterize the liver biopsy and to assess liver fibrosis by non-invasive methods (for example, elastometry or fibrosis indexes) (see Appendix D).

Pangenotypic — a characteristic of a drug or group of drugs that are effective against all the most common genotypes of the hepatitis C virus.

Sustained virological response (SVR) — undetectable HCV RNA after treatment completiont.

Viral load — the amount of viral RNA in the blood, measured in IU/ml [1].

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

The causative agent of CHC is HCV, which is a small hepatotropic RNA virus from the Family Flaviviridae. The virus formed of a nucleocapsid consisting of a core (nuclear) protein (HCVcAg) and a single-stranded (+) RNA, and a protein-lipid shell composed of human apolipoprotein E (apoE), and viral proteins E1 and E2. The viral genome encodes 10 different proteins — 3 structural and 7 non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) [2].

There are 8 genotypes (GT) [3], which are indicated by Arabic numerals from 1 to 8, and several dozen subtypes of HCV, which are indicated by Latin letters. The most clinically important are the GT1 subtypes: a and b. Genotypes and subtypes differ in sequences by about 30 and 20 %, respectively. The variability of the virus genome causes changes in the structure of antigenic determinants that determine the production of specific antibodies. This prevents the elimination of the virus from the body and is the reason that the creation of an effective HCV vaccine failed [4, 5].

Infection in a larger proportion of cases (55–85 %) leads to a chronic course of the disease and in about a quarter of patients leads to the development of LC over the following decades, which, in turn, can be a basis for HCC [6]. Quite often, due to the predominant asymptomatic course of infection, the disease is first manifested by complications of cirrhosis.

The leading pathogenetic mechanism in CHC is a violation of the interaction of immune cells with infected hepatocytes. Damage to the liver tissue is largely the result of the implementation of the immune response in the focus of inflammation, and not the cytopathic action of the virus [7]. Immunocompetent cells accumulate in the liver, some of which (NK cells, cytotoxic T-lymphocytes) have high cytotoxicity and the ability to damage hepatocytes [8]. As a result of contact of infected hepatocytes with cytotoxic T-lymphocytes (a component of the adaptive immune response), apoptosis is triggered. There is a deficiency of the T-system, depression of macrophages, weakening of the interferonogenesis system, lack of specific antibody against virus antigens, which ultimately disrupts the adequate recognition and elimination by the immune system of virus antigens on the surface of hepatocytes [8–11].

In patients with a pronounced T-cell response, complete elimination of HCV occurs after resolving acute hepatitis C. Due to the interaction of the virus and the immune system, the activity of cytotoxic T-lymphocytes is inhibited by virus proteins. As a result, in CHC immunological tolerance to the virus is formed [12].

The action of the virus and the immunological reactions causes not only liver injury, but also to other organs and tissues. The concept of extrahepatic (systemic) signs is the possibility of viral replication outside the liver, namely in tissues of lymphoid and non-lymphoid origin [13]. The reproduction of the virus in immunocompetent cells (lymphocytes) leads to a violation of their immunological function. Preservation of HCV in monocytes is the main cause of reinfection after liver transplantation in patients with severe forms of CHC [10].

Among the host factors affecting the outcome and course of CHC, age at the time of infection, alcohol abuse, co-infection with hepatotropic viruses, lipid metabolism disorders, etc. are important [14, 15].

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

Approximately in 1 % of the world population (about 71 million people) antibodies to HCV

(anti-HCV) are detected, among which 2/3 are chronically infected, and 1/3 recovered independently or as a result of antiviral treatment. The disease is more common in Africa and Asia (almost 3 % of the population), while in the Americas and Europe it is detected in 1.5–2.0 % [17]. The reliable prevalence of CHC in the Russian Federation remains unknown, the estimated number of patients may reach 4.9 million [16]. According to official governmental reports (data on 01.01.2017) there were 591,830 patients with CHC in Russian Federation [16].

In Russia, the most common are GT 1 (52.6 %, of which 3.7 % are subtype 1a and 48.9 % are subtype 1b) and GT 3 (39.6 %), GT 2 is much less common (7.8 %). Genotypes 4–6 occur in less than 0.01 % of cases, GT 7 and 8 are extremely rare [16]. With the advent of pangenotypic regimens for antiviral treatment, the clinical significance of HCV GT is gradually lost, but there are still a number of genotype-specific drugs, before the use of which it is necessary to clarify genotype.

The source of infection is an infected person. The most significant is the parenteral route of transmission (with the use of intravenous illicit drugs, medical manipulations, traumatic cosmetic procedures, including manicure and pedicure, tattooing and piercing), much less often — sexual and vertical transmission routes [18].

The risk of occupational infection of health workers with an accidental injection with infected blood is about 1.8 %. If the patient's blood gets on the damaged skin or intact mucous membranes of the medical worker, the risk of infection is much less, and its contact with intact skin is safe. In this regard, the risk of infection for medical personnel is small. The risk of infection of a patient from an infected health worker is extremely small [18]. The risk of perinatal transmission is 5–10 % and depends little on the method of delivery, but increases in the presence of HIV co-infection in the mother to 14–16 % [18]. The low concentration of the virus in the secretions of the sex glands and organs determines the low risk of its sexual transmission: about 0.5 % per year with unprotected sexual contact in a monogamous heterosexual couple, about 0.4–1.8 % per year among sex workers [19], about 0.8 % per year among men who have sex with men with monoinfection of HCV (with HIV co-infection, it is 4 times higher) [20].

HCV has a relatively low resistance to environmental factors. It is known that the virus is resistant to heating up to 50 °C, its inactivation occurs after 30 minutes at a temperature of 60 °C and after 2 minutes at a temperature of 100°C. The virus is sensitive to ultraviolet irradiation and exposure to lipid solvents [21].

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

B18.2 — chronic hepatitis C.

The previously used Z22.5 code for viral hepatitis carriers has been removed from the latest revision of ICD 10.

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

The disease is classified depending on the HCV GT, as well as the presence of CP and extrahepatic manifestations.

1.5.1. By stage:

0 — without fibrosis;
1 — mild fibrosis;
2 — moderate fibrosis;
3 — pronounced fibrosis;
4 — severe fibrosis.

1.5.2. By HCV genotype:

1 — genotype 1;
- genotype 1a,
- genotype 1b;

2 — genotype 2 (including 2k1b);
3 — genotype 3;
4 — genotype 4;
5 — genotype 5;
6 — genotype 6;
7 — genotype 7;
8 — genotype 8.

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

In most patients, the disease is asymptomatic and is detected during examination as part of a medical examination, prehospital preparation, when visiting a gastroenterologist for dyspepsia (usually not directly related to the presence of CHC) and other specialists (gynecologists, urologists, dentists, etc.). From the time of infection to diagnosis, it can take several years. In some cases, the first manifestation of the disease is B-cell lymphoproliferative or immunologically determined extrahepatic diseases (cryoglobulinemic vasculitis, including Raynaud's syndrome; interstitial lung diseases; glomerulonephritis; Sjögren's syndrome; arthritis, etc.). In a sufficient number of patients, the diagnosis is established only after the manifestation of complications of cirrhosis: variceal bleeding and the development of ascites [22, 23].

On physical examination in the absence of LC, there are usually no pathological manifestations [22].

The activity of transaminases can be both increased and within the reference values. In some cases, there is a periodic increase in ALT activity. Anti-HCV and HCV RNA are detected in the blood. ALT activity within normal values does not indicate the absence of changes in the liver, and patients cannot be considered as "healthy carriers". It has been shown that 30–50 % of cases in such patients can be diagnosed with LC [24, 25]. Often in the initial stage of compensated LC, only weight loss, weakness, decreased performance are noted. Examination reveals hepatomegaly and splenomegaly. However, in 20 % of patients in the initial stage of LC, it is asymptomatic, and it is detected, as a rule, by chance during a routine examination or examination for another disease.

Cirrhosis develops in 25–35 % of cases of CHC. The risk accounts 7.3 % per year (5.1–9.5 %). In many patients LC is first diagnosed by histological examination of liver biopsy. Decompensation rate is 5.5 % per year. The probability of developing portal hypertension syndrome within a year in patients with compensated LC is 3.6 %, hepatic encephalopathy — 0.4 %, HCC — 1.5 % [24, 26, 27].

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

Criteria for the diagnosis of CHC

The diagnosis of CHC is established on the basis of the presence of antibodies to the hepatitis C virus (Determination of total antibodies of classes M and G (anti-HCV IgG and anti-HCV IgM) to the hepatitis C virus (Hepatitis C virus) in the blood, further everywhere in the text — anti-HCV) and hepatitis C virus RNA (Determination of hepatitis C virus RNA in the blood by qualitative PCR, further everywhere in the text — HCV RNA) or nuclear antigen HCV (Determination of the Core antigen of hepatitis C virus (Hepatitis C virus) in the blood, then everywhere in the text — HCVcAg) for more than 6 months [1].

2.1. Complaints and history

There are no specific complaints for CHC. The disease is often asymptomatic, and may manifest as complications of LC (ascites, bleeding from the EV, hepatic encephalopathy) [28]. In some cases, the first manifestations of the disease are immunologically determined extrahepatic manifestations [23].

2.2. Physical examination

Physical examination, as a rule, does not reveal any changes. Perhaps the presence of signs of LC (ascites, "liver palms", veins on the abdominal wall, edema, splenomegaly). With the development of immunologically determined extrahepatic manifestations, corresponding changes occur [23].

2.3. Laboratory diagnostic tests

At the screening stage

Screening for the presence of CHC is based on the detection of anti-HCV. If anti-HCV is detected, it is imperative to perform an HCV RNA test. If an HCV RNA test is not available, it is permissible to perform an HCVcAg test. This antigen in serum or blood plasma is also a marker of HCV replication. HCVcAg analysis less sensitive than HCV RNA (the lower detection limit is equivalent to approximately 500-3000 IU/mL of HCV RNA, depending on HCV GT [28, 29]). In rare cases, HCVcAg is not detected in detectable HCV RNA [30].

• Anti-HCV screening in high-risk individuals is recommended to identify potentially infected people [1, 31–33].

Grade of evidence C
(level of evidence 5)

Comments: the high-risk group is established, as a rule, according to the patient (place of work, recipient in the anamnesis, introduction of injecting drugs, sexual partners, family history, etc.).

The high-risk group includes:

- *Pregnant woman;*
- *Recipients of blood and its components, organs and tissues;*
- *Personnel of medical organizations;*
- *Patients of centers and departments of hemodialysis, kidney transplantation, cardiovascular and pulmonary surgery, hematology;*
- *People and staff in boarding schools;*
- *Contact persons in foci of acute and chronic hepatitis C;*
- *Intravenous drug users and their sexual partners;*
- *Sexual service providers and their sexual partners;*
- *Men who have sex with men;*
- *Individuals with a number of sexual partners;*
- *Persons who have had a tattoo;*
- *Persons in prisonsy;*
- *Donors of blood (its components), organs and tissues, sperm;*
- *Patients with immunodeficiency (patients with oncological diseases, patients*

on hemodialysis, patients on treatment with immunosuppressants, etc.);

• *Patients with liver diseases of unclear etiology (in the process of primary clinical and laboratory examination).*

All patients with identified anti-HCV antibodies are advised to have an HCV RNA test or HCVcAg (if the former is not available) to confirm the presence of a current infection [1, 34].

Grade of evidence C
(level of evidence 5)

• All patients with detected anti-HCV antibodies and negative HCV RNA (or HCVcAg in case of unavailability of the former) are recommended to re-analyze HCV RNA at 12 and 24 weeks in order to confirm or refute the presence of CHC [1].

Grade of evidence A
(level of evidence 5)

Comments: The presence of anti-HCV antibodies in combination with HCV RNA (or HCVcAg) is characteristic of both patients with CHC and patients with acute hepatitis C. The concentration of HCV RNA (or HCVcAg) in patients with acute hepatitis C can fluctuate significantly, up to an undetectable level. Thus, patients with undetectable HCV RNA (or HCVcAg) need to re-analyze HCV RNA (or HCVcAgAg).) 12 and 24 weeks after the negative result, in order to verify the clearance of HCV (self-recovery from acute hepatitis C) or to confirm the development of CHC.

At the stage of diagnosis:

• Determination of the genotype of the hepatitis C virus (hereinafter everywhere in the text — GT HCV) is recommended only for patients with CHC to plan a genotype-specific regimen of antiviral treatment (AVT) [1, 35].

Grade of evidence A
(level of evidence 5)

Comments: HCV GT is only relevant when planning genotype-specific antiviral drugs. With the availability of pangenotypic drugs, this test is not required.

• All patients with HCV-related LC and / or signs of extrahepatic manifestations (lymphoproliferative diseases) are recommended to perform a complete blood count [23, 36–38].

Grade of evidence C
(level of evidence 4)

Comments: the course of CHC can affect the cellular composition of the blood, but there is no convincing evidence of such changes in the absence of LC and lymphoproliferative diseases induced by HCV. In the case of LC, thrombocytopenia of varying severity is most often observed, less often other variants of cytopenia.

• All patients with CHC are recommended to perform a biochemical blood test to determine the activity of transaminases (alanine aminotransferase, aspartate aminotransferase), the severity of liver damage, and assess liver and kidney function [39–41].

Grade of evidence C
(level of evidence 4)

*Comments: in the absence of signs of LC, the clinical significance of the activity of transaminases and other indicators of liver function (bilirubin, albumin) is low. It becomes more important if there is a combined pathology of the liver. In patients with LC, the severity of hepatocyte damage and signs of decompensation are crucial in choosing the patient management tactics, antiviral drugs, prognosis of the course of the disease [39]. In addition, ALT and AST can be used to independently assess the severity of liver fibrosis (e.g., APRI, FIB-4) in the absence of an instrumental examination [42] (see Appendix D). Evaluation of renal function (creatinine) is necessary when planning antiviral regimens containing sofosbuvir*** [40, 41].

• All patients with HCV-related LC are recommended to determine prothrombin (thromboplastin) time in the blood or plasma to assess liver function [43, 44].

Grade of evidence C
(level of evidence 5)

• Assessment of the alpha-fetoprotein (AFP) level in the blood serum of patients with CHC with advanced liver fibrosis and cirrhosis (METAVIR score F3 and F4) is recommended for the timely diagnosis of HCC [44–46].

Grade of evidence A
(level of evidence 1)

Comments: The risk of HCC development at the LC stage is approximately 1–5 % per year. The probability of death within the first year after diagnosis in patients with HCC is 33 %.

At the stage of AVT:

•Laboratory monitoring is not recommended for patients with CHC without LC during AVT without ribavirin** [1, 47].

Grade of evidence B
(level of evidence 2)

*Comment: current antiviral drugs have high safety and efficacy, and therefore there is no need for laboratory monitoring during AVT without the use of ribavirin**.*

• When using RBV**, it is recommended to perform a complete blood count every 2–4 weeks in order to rule out a frequent side effect of the drug — anemia [1, 47].

Grade of evidence C
(level of evidence 5)

• It is not recommended to determine HCV RNA during AVT to assess its efficacy [47, 48] (see Appendix B).

Grade of evidence C
(level of evidence 5)

Comment: there is no connection between the rate of HCV elimination during AVT and the rate of SVR, and therefore there is no need to control HCV RNA during treatment [48].

At the stage of post treatment observation:

• It is not recommended to use anti-HCV assay in patients who have recovered from CHC after AVT to control HCV reinfection [49–51].

Grade of evidence C
(level of evidence 5)

Comment: After successful AVT anti-HCV persists for a long time in the vast majority of cases, so this analysis cannot be used to determine reinfection in patients with experience of HCV elimination. The proportion of patients in whom anti-HCV gradually disappears is very small, and the duration of this disappearance is unknown.

• All patients who have received AVT are recommended to be tested for HCV RNA 12 weeks after the end of the AVT to assess its efficacy (SVR12) [44, 47, 48] (see Appendix B).

Grade of evidence C
(level of evidence 5)

Comment: The absence of HCV RNA 12 weeks after the end of AVT corresponds to a cure of CHC, since late relapse occurs in less than 0.2 % of cases [48].

• It is recommended to determine the AFP level in patients with advanced liver fibrosis (METAVIR F3) and with LC every six months for the diagnosis of HCC [45, 46].

Grade of evidence A
(level of evidence 1)

Commentary: The risk of HCC development at the LC stage is about 1–5 % per year. The probability of death within the first year after diagnosis in patients with HCC is 33 %.

2.4. Instrumental diagnostic studies

At the stage of diagnosis:

• All patients with CHC are recommended to perform abdominal ultrasound to detect signs of LC and HCC [52, 53].

Grade of evidence A
(level of evidence 2)

Comments: Abdominal ultrasound is performed for the diagnosis of HCC, signs of portal hypertension (enlargement of the spleen, dilation of the veins of the portal system), ascites, exclusion of concomitant pathology of the gastrointestinal tract, which in some cases can be decisive in determining the stage of the disease and treatment tactics. LC and HCC can be asymptomatic and detected only by ultrasound. If a focal liver lesion suspicious of HCC is detected, studies should be continued in accordance with clinical recommendations for the diagnosis and treatment of HCC.

• All patients with CHC are advised to perform a non-invasive diagnosis of fibrosis in order to determine the tactics of AVT and further management of the patient (in the case of LC) [54–58].

Grade of evidence A
(level of evidence 1)

Comments: non-invasive diagnostics can determine the stage of fibrosis with high accuracy. It can be performed using liver stiffness measurement (to be performed on a validated machine), or using serum tests. If liver stiffness measurement (elastometry) is not available, non-commercial calculation tests based on the results of laboratory examination (for example, the calculation of APRI, FIB-4 indices, see Annexes G2, G3) can be used.

• If conflicting non-invasive diagnostic data are obtained, it is recommended to consider percutaneous liver biopsy in order to determine the tactics of the AVT and further management of the patient (in the case of LC) [1].

Grade of evidence C
(level of evidence 5)

Comments: Liver biopsy is an invasive procedure with a risk of complications, so it should be performed only if it is not possible to obtain a result using non-invasive methods [1].

• Esophagogastroduodenoscopy (EGD) is recommended for patients with HCV-related cirrhosis to assess the presence and extent of oesophageal and gastric varices [59–61].

Grade of evidence C
(level of evidence 4)

Comments: Endoscopy is performed to diagnose the degree of oesophageal and gastric varices, as well as when applying clips and ligatures during bleeding or its prevention from the veins of the esophagus in patients with LC. It is possible to carry out the procedure under anesthesia, which requires prior consultation and accompaniment of an anesthesiologist.

• Abdominal computed tomography with intravenous bolus contrast or magnetic resonance imaging of the abdominal organs with intravenous contrast is recommended for patients with CHC if a focal liver lesion is detected by abdominal ultrasound to clarify its nature [62–65].

Grade of evidence C
(level of evidence 5)

At the stage of post treatment observation:

• It is recommended to perform a non-invasive diagnosis of the stage of liver fibrosis (liver elastometry, if it is not available — serum non-commercial tests APRI, FIB-4) in patients with CHC once a year for dynamic observation [54, 55, 57, 66].

Grade of evidence A
(level of evidence 1)

• It is recommended to perform EGD in patients with HCV-related LC for dynamic monitoring once a year [59–61, 67].

Grade of evidence C
(level of evidence 4)

• After recovery from CVHC, patients with advanced liver fibrosis (METAVIR F3) or LC are recommended to undergo a lifelong screening examination for the early detection of HCC (abdominal ultrasound every 6 months) [53].

Grade of evidence A
(level of evidence 1)

Comments: these patients still have a risk of developing HCC, despite the elimination of the virus, so they are recommended to conduct a preventive examination for its early detection.

3. Treatment, including medication and non-drug therapy, diet, anesthesia, medical indications and contraindications to the use of treatment methods

The goal of CHC treatment is to eliminate HCV to prevent complications of HCV (including LC, HCC, death), improve quality of life, and prevent further transmission of HCV in the population. The hepatitis C virus does not form highly stable intracellular forms of genetic material, so it can be eliminated from the body completely [1]. An indicator of the elimination of the virus from the body is the persistent achievement of an undetectable level of virus RNA in the blood, which is evaluated 12 weeks after the end of therapy (SVR12) [29, 30].

The choice of treatment regimen is influenced by the following factors [68]:

• the stage of liver fibrosis, the presence of LC and its severity;
• HCV GT;
• the presence of some concomitant diseases;
• experience of the previous AVT (if any);
• medications for concomitant pathology.

3.1. Indications for initiation of antiviral therapy

• Antiviral treatment is recommended for all patients with CHC, regardless of the presence of LC, in order to cure infection (HCV eradication) [1, 69] (see also Appendix A3).

Grade of evidence A
(level of evidence 1)

Comments: treatment of CHC is indicated for all patients, since highly effective and safe drugs are currently used that allow to achieve SVR in the vast majority of cases.

*Direct-acting antivirals (DAAs) are used to treat CHC. Those of them that are included in the list of vital and essential drugs are marked with the sign**. DAAs are inhibitors of various non-structural proteins of the virus. The second root of the name of the DAA indicates which specific protein it inhibits: "-previr" — NS3 / NS4A, "-asvir" — NS5A, "-buvir" — NS5B. The choice of drugs for treatment and the duration of treatment depend on the stage of fibrosis, the presence and class of LC, virus GT, the experience of previous antiviral therapy, the presence of concomitant diseases (in particular, chronic kidney disease (CKD)), some concomitant drugs. Depending on the effectiveness of drugs in various GT, pangenotypic schemes (effective for all GT of the virus) and genotype-specific (effective only for certain HCV GT) are distinguished. Table 1 presents drugs and their components used in the Russian Federation.*

• Immediate therapy is recommended to be considered primarily in patients:
• with HCV-related LC (including decompensated LC);
• with severe fibrosis (METAVIR F3);
• with clinically significant extrahepatic manifestations;
• with recurrence of CHC after liver transplantation;
• with the risk of rapid progression of liver disease due to concomitant diseases (chronic viral hepatitis B, HIV infection, diabetes mellitus, etc., after transplantation of organs other than the liver);
• with a high risk of transmission [1, 69].

Grade of evidence A
(level of evidence 1)

Prior to starting treatment with a DAA, a full and detailed drug history should be taken including all prescribed medications. It is recommended to check the interaction of the drugs using any special resource (for example, https://www.hep-druginteractions.org). If a significant interaction is detected, it is recommended to replace the regimen or drug that the patient takes in the treatment of a concomitant disease. If this is not possible, the decision should be made on a case-by-case basis, assessing the benefit-risk ratio of this combination and the possible consequences of its use [70].

Table 1. Components that are part of direct-acting antivirals and DAAs, approved for use in the Russian Federation (presented in alphabetical order)

Таблица 1. Компоненты, входящие в состав лекарственных средств прямого противовирусного действия, и лекарственные средства прямого противовирусного действия, одобренные для применения в РФ, (представлены в алфавитном порядке)

NS3/4A inhibitors Ингибирующие NS3/4A	NS5A inhibitors Ингибирующие NS5A	NS5B inhibitors Ингибирующие NS5B
· Glecaprevir (GLE)[a] · Глекапревир (ГЛЕ)[a]	· Velpatasvir (VEL)[a]· Велпатасвир (ВЕЛ)[a]	· Dasabuvir (DSV)[a] · Дасабувир (ДСВ)[a]
· Grazoprevir (GRA)[a] · Гразопревир (ГРА)[a]	· Daclatasvir** (DAC**)· Даклатасвир** (ДАК**)	· Sofosbuvir** (SOF**)· Софосбувир** (СОФ**)
· Narlaprevir** (NRV**) · Нарлапревир** (НРВ**)	· Ledipasvir (LED)[a] · Ледипасвир (ЛЕД)[a]	
· Paritaprevir (PTV)[a]· Паритапревир (ПТВ)[a]	· Ombitasvir (OBV)[a]· Омбитасвир (ОБВ)[a]	
	· Pibrentasvir (PIB)[a]· Пибрентасвир (ПИБ)[a]	
	· Elbasvir (ELB)[a] · Элбасвир (ЭЛБ)[a]	

Fixed combinations of DAAs:
· Velpatasvir + sofosbuvir** (VEL+SOF**)
· Glecaprevir + pibrentasvir** (GLE+PIB**)
· Grazoprevir + elbasvir** (GRA+ELB**)
· Dasabuvir; ombitasvir + paritaprevir + ritonavirb** (DSV; OBV+PTV/r**)
· Ledipasvir + sofosbuvir (LED+SOF)
Note: a — part of the combined drugs; b — ritonavir** (RTV**) — pharmacokinetic booster which does not have antiviral activity and is used with NRV** and PTV to increase their concentration in the blood.
Фиксированные комбинированные ПППД:
· велпатасвир + софосбувир** (ВЕЛ+СОФ**),
· глекапревир + пибрентасвир** (ГЛЕ+ПИБ**),
· гразопревир + элбасвир** (ГРА+ЭЛБ**),
· дасабувир; омбитасвир + паритапревир + ритонавирб** (ДСВ; ОБВ+ПТВ/р**),
· ледипасвир + софосбувир (ЛЕД+СОФ).
Примечание: а — входят в состав комбинированных препаратов; б — ритонавир** (РТВ**) — фармакокинетический бустер, не обладает противовирусной активностью, используется с НРВ** и ПТВ для увеличения их концентрации в крови.

Grade of evidence C
(level of evidence 4)

Comments: Most DAAs are safe, but their pharmacokinetic features can lead to significant interactions with other drugs taken by the patient.

3.2. Treatment of patients without LC and with compensated LC

Since experience in previous AVT and the presence LC significantly affects the efficacy of AVT, drug regimen and duration differ depending on the presence of these factors. In this regard, patients with CHC are usually divided into several groups:

· Treatment-naïve patients without LC;
· Treatment-naïve patients with compensated LC;
· Patients who did not responded to previous AVT (PegIFN** + RBV** ± SOF** or SOF** + RBV**) without LC;
· Patients who did not respond to previous AVT (PegIFN** + RBV** ± SOF** or SOF** + RBV**) with compensated LC [71–75].

Treatment of patients with decompensated LC is discussed separately in section 3.9 “Liver transplantation” and in Appendix A3.

The principles of treatment after an unsuccessful course of DAAs (NS3/4A inhibitors and/or NS5A inhibitors) are discussed in section 3.4.

• Treatment-naïve patients patients without LC and without liver transplantation are recommended to one of the alternative schemes according to Table 2:

– Velpatasvir + Sofosbuvir** [76–79]
Grade of evidence A
(level of evidence 2)
– Glecaprevir + Pibrentasvir** [80]
Grade of evidence A
(level of evidence 2)
– Daclatasvir** + Sofosbuvir** [81–86]
Grade of evidence A
(level of evidence 3)
– Grazoprevir + Elbasvir** [88–92]
Grade of evidence A
(level of evidence 2)
– Daclatasvir** + Narlaprevir** + Ritonavir** [93]
Grade of evidence C
(level of evidence 4)
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** in patients with genotype 1b,
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** + Ribavirin** in patients with genotype 1a [94, 95]
Grade of evidence A
(level of evidence 2)
– Ledipasvir + Sofosbuvir [96, 97]
Grade of evidence A
(level of evidence 3)
– Narlaprevir** + Sofosbuvir** + Ritonavir** [98, 99]
Grade of evidence B
(level of evidence 3)

• Treatment-naïve patients with compensated LC — schemes according to Table 3:

– Velpatasvir + Sofosbuvir** [76, 79]
Grade of evidence A
(level of evidence 3)
– Glecaprevir + Pibrentasvir** [100–103]
Grade of evidence A
(level of evidence 4)
– Daclatasvir** + Sofosbuvir** in patients with genotype 1, 2 and 4 [104–106]
Grade of evidence A
(level of evidence 3)
– Daclatasvir** + Sofosbuvir** + Ribavirin** in patients with genotype 3 [106, 107]
Grade of evidence A
(level of evidence 3)
– Grazoprevir + Elbasvir** [108–111]
Grade of evidence A
(level of evidence 2)
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** in patients with genotype 1b,
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** + Ribavirin** in patients with genotype 1a [112, 113]
Grade of evidence A
(level of evidence 2)
– Ledipasvir + Sofosbuvir or Ledipasvir + Sofosbuvir + Ribavirin** [114–122]
Grade of evidence A
(level of evidence 3)

• Treatment of patients with HCV infection without cirrhosis who did not respond to therapy PegIFN** + RBV** ± SOF** or SOF** + RBV** is recommended to be carried out according to one of the alternative schemes (Table 4):

– Velpatasvir + Sofosbuvir** [76, 79]
Grade of evidence A
(level of evidence 3)
– Glecaprevir + Pibrentasvir** [100–102]
Grade of evidence A
(level of evidence 3)
– Daclatasvir** + Sofosbuvir** [84, 104, 105, 123]
Grade of evidence A
(level of evidence 3)
– Grazoprevir + Elbasvir** [87, 88, 90, 111]
Grade of evidence A
(level of evidence 2)
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** for genotype 1b,
– Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** + Ribavirin** for genotype 1a [112, 113]
Grade of evidence A
(level of evidence 2)
– Ledipasvir + Sofosbuvir or Ledipasvir + Sofosbuvir + Ribavirin** [114–122]
Grade of evidence A
(level of evidence 3)

• Treatment of patients with HCV infection and compensated cirrhosis who did not respond to therapy PegIFN** + RBV** ± SOF** or SOF** + RBV** is recommended to be carried out according to one of the alternative schemes (Table 5):

– Velpatasvir + Sofosbuvir** [76, 79]
Grade of evidence A
(level of evidence 2)
– Glecaprevir + Pibrentasvir** [100–102]
Grade of evidence A
(level of evidence 3)
– Daclatasvir** + Sofosbuvir** [101, 125, 126]
Grade of evidence A
(level of evidence 3)
– Daclatasvir** + Sofosbuvir** + Ribavirin** [84, 108, 124, 127]
Grade of evidence A
(level of evidence 2)
– Grazoprevir + Elbasvir** [87, 88]

Table 2. AVT schemes for treatment-naïve patients and without LC, depending on the genotype (drugs are presented in alphabetical order)

Таблица 2. Схемы ПВТ ХВГС для пациентов без предшествующего опыта ПВТ и без цирроза печени в зависимости от генотипа (лекарственные средства представлены в алфавитном порядке)

	Pangenotypic treatment regimens Пангенотипные схемы лечения			Genotype-specific treatment regimens Генотип-специфичные схемы лечения				
ГТ GT	VEL +SOF** ВЕЛ+ СОФ**	GLE +PIB** ГЛЕ+ ПИБ**	DAC** +SOF** ДАК**+ СОФ**	GRAS+ELB** ГРА+ЭЛБ**	DAC** +NRV**/r** ДАК**+ НРВ**/р**	DSV; OBV+ PTV/r** ДСВ; ОБВ+ ПТВ/р**	LED+ SOF ЛЕД+ СОФ	NRV**/r**+ SOF** НРВ**/р**+ СОФ**
1a	12 weeks 12 нед.	8 weeks 8 нед.	12 weeks 12 нед.	12/16 weeks[а] 12/16 нед.[а]	-	12 weeks + RBV** 12 нед. + РБВ**	8 weeks 8 нед.	12 weeks 12 нед. #8 weeks[в] #8 нед.[в]
1b				8/12 weeks[б] 8/12 нед.[б]	12 weeks 12 нед.	8/12 weeks[б] 8/12 нед.[б]		
2				–	–	–	–	–
3				12 weeks + SOF** 12 нед. + СОФ**	–	–	–	–
4				12/16 weeks[а] 12/16 нед.[а]	–	–	12 weeks 12 нед.	–

Note:

VEL+SOF ** — velpatasvir + sofosbuvir** (100/400 mg) one tablet once daily;

GLE+PIB** — glecaprevir + pibrentasvir** (3 tab. simultaneously, 100/40 mg each) once a day;

DAC**+SOF** — daclatasvir** 60 mg one tablet once daily + sofosbuvir** 400 mg one tablet once daily;

GRA+ELB ** — grazoprevir + elbasvir** 100/50 mg one tablet once daily;

DAC**+NRV**/r** — daclatasvir** 60 mg once a day + narlaprevir** 200 mg once a day (2 tab. simultaneously, 100 mg each) + ritonavir** 100 mg once a day;

DSV; OBV+PTV/r** — dasabuvir (1 tab. 250 mg twice a day); ombitasvir + paritaprevir + ritonavir** (2 tab. simultaneously once a day, 12.5/75/50 mg each);

LED+SOF — ledipasvir + sofosbuvir 90/400 mg one tablet once daily;

NRV**/r**+SOF** — narlaprevir** 200 mg once a day (2 tab. simultaneously, 100 mg each) + ritonavir** 100 mg once a day + sofosbuvir** 400 mg one tablet once daily;

a — with viral load of not more than 800,000 IU/ml, the treatment period is 12 weeks; A 16-week course with regimen containing RBV** should be considered for HCV RNA > 800,000 ME/mL and/or NS5A polymorphisms;

b — in patients with mild fibrosis (METAVIR F0–2) 8 weeks, with advanced fibrosis and cirrhosis (METAVIR F3–F4) — 12 weeks.

c — in patients with mild fibrosis (F0–F2) and viral load less than 1,000,000 IU/ml, a duration of 8 weeks can be considered by decision of the medical commission.

Примечание:

ВЕЛ+СОФ** — велпатасвир + софосбувир** (100/400 мг) 1 таб. 1 р/д;

ГЛЕ+ПИБ** — глекапревир + пибрентасвир** (3 таб. одновременно по 100/40 мг каждая) 1 р/д;

ДАК**+СОФ** — даклатасвир** 60 мг 1 таб. 1 р/д + софосбувир** 400 мг 1 таб. 1 р/д;

ГРА+ЭЛБ** — гразопревир + элбасвир** 100/50 мг 1 таб. 1 р/д;

ДАК**+НРВ**/р** — даклатасвир** 60 мг 1р/д + нарлапревир** 200 мг 1 р/д (2 таб. одновременно по 100 мг каждая) + ритонавир** 100 мг 1 р/д;

ДСВ; ОБВ+ПТВ/р** — дасабувир (1 таб. по 250 мг 2 р/д); омбитасвир + паритапревир + ритонавир** (2 таб. одновременно 1 р/д по 12,5/75/50 мг каждая);

ЛЕД+СОФ — ледипасвир + софосбувир 90/400 мг 1 таб. 1 р/д;

НРВ**/р**+СОФ** — нарлапревир** 200 мг 1 р/д (2 таб. одновременно по 100 мг каждая) + ритонавир** 100 мг 1 р/д + софосбувир** 400 мг 1 таб. 1 р/д;

а — при ВН не более 800 000 МЕ/мл срок лечения 12 недель; 16-недельный курс совместно с РБВ** следует рассмотреть при ВН ВГС > 800 000 МЕ/мл и/или при наличии полиморфизмов NS5A;

б — у пациентов со слабовыраженным фиброзом (F0–2) 8 недель, с фиброзом F3–F4 по METAVIR — 12 недель;

в — у пациентов со слабовыраженным фиброзом (F0–2) и ВН менее 1 000 000 МЕ/мл можно рассмотреть длительность 8 недель по решению врачебной комиссии.

Table 3. AVT schemes for treatment-naïve patients patients with compensated LC depending on the genotype (drugs are presented in alphabetical order)

Таблица 3. Схемы ПВТ ХВГС для пациентов с компенсированным циррозом печени без предшествующего опыта ПВТ в зависимости от генотипа (лекарственные средства представлены в алфавитном порядке)

	Pangenotypic treatment regimens Пангенотипные схемы лечения			Genotype-specific treatment regimens Генотип-специфичные схемы лечения		
GT ГТ	VEL+ SOF** ВЕЛ+ СОФ**	GLE+ PIB** ГЛЕ+ ПИБ**	DAC** +SOF** ДАК** +СОФ**	GRAS+ ELB** ГРА+ ЭЛБ**	DSV; OBV+PTV/r** ДСВ; ОБВ+ПТВ/р**	LED+SOF ЛЕД+СОФ
1a	12 weeks[b] 12 нед. [б]	8 weeks 8 нед.	12 нед. 12 weeks	12/16 weeks[a] 12/16 нед.[а]	24 weeks + RBV** 24 нед. + РБВ**	12 weeks + RBV** 12 нед + РБВ** 24 weeks without RBV** 24 нед. без РБВ**
1b				12 weeks 12 нед.	12 weeks 12 нед.	
2				–	–	–
3			–	12 weeks + SOF[b] 12 нед. + СОФ[б]	–	24 weeks + RBV[b] 24 нед. + РБВ[в]
4			12 weeks 12 нед.	12/16 weeks[a] 12/16 нед.[а]	–	12 weeks + RBV** 12 нед. + РБВ** 24 weeks without RBV** 24 нед. без РБВ**

Note:

VEL+SOF ** — velpatasvir + sofosbuvir** (100/400 mg) 1 tab./day;

GLE+PIB** — glecaprevir + pibrentasvir** (3 tab. simultaneously, 100/40 mg each) per day;

DAC**+SOF** — daclatasvir** 60 mg 1 tab. 1 p/d + sofosbuvir** 400 mg 1 tab. per day;

GRA+ELB** — grazoprevir + elbasvir** 100/50 mg 1 tab. per day;

DSV; OBV+PTV/r** — dasabuvir (1 tab. 250 mg 2 times per day); ombitasvir + paritaprevir + ritonavir** (2 tab. simultaneously per day, 12.5/75/50 mg each);

LED+SOF — ledipasvir + sofosbuvir 90/400 mg 1 tab. per day;

a — if the HCV RNA level ≤ 800,000 U/ml, the treatment period is 12 weeks; 16-week course with RBV** should be considered for the HCV RNA level > 800,000 U/mL and/or NS5A polymorphisms;

b — the addition of RBV** may be considered for genotype 3;

c — in a case of unavailability of other treatment regimens.

Примечание:

ВЕЛ+СОФ** — велпатасвир + софосбувир** (100/400 мг) 1 таб. 1 р/д;

ГЛЕ+ПИБ** — глекапревир + пибрентасвир** (3 таб. одновременно по 100/40 мг каждая) 1 р/д;

ДАК**+СОФ** — даклатасвир** 60 мг 1 таб. 1 р/д + софосбувир** 400 мг 1 таб. 1 р/д;

ГРА+ЭЛБ** — гразопревир + элбасвир** 100/50 мг 1 таб. 1 р/д;

ДСВ; ОБВ+ПТВ/р** — дасабувир (1 таб. по 250 мг 2 р/д); омбитасвир + паритапревир + ритонавир** (2 таб. одновременно 1 р/д по 12,5/75/50 мг каждая);

ЛЕД+СОФ — ледипасвир + софосбувир 90/400 мг 1 таб. 1 р/д;

а — при ВН не более 800 000 МЕ/мл срок лечения 12 недель; 16-недельный курс совместно с РБВ** следует рассмотреть при ВН ВГС > 800 000 МЕ/мл и/или при наличии полиморфизмов NS5A;

б — для ГТ 3 можно рассмотреть добавление РБВ**;

в — в случае недоступности иных схем лечения.

Grade of evidence A
(level of evidence 2)

— Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** for genotype 1b,

— Dasabuvir; Ombitasvir + Paritaprevir + Ritonavir** + Ribavirin** for genotype 1a [94, 95]

Grade of evidence A
(level of evidence 2)

— Ledipasvir + Sofosbuvir or Ledipasvir + Sofosbuvir + Ribavirin** [96, 116, 118–122]

Grade of evidence A
(level of evidence 3)

Table 4. HCV infection treatment schemes for patients without cirrhosis who have not responded to therapy PegIFN** + RBV** ± SOF** or SOF** + RBV** depending on the genotype

Таблица 4. Схемы ПВТ ХВГС для пациентов, не ответивших на предшествующую терапию ПегИФН** + РБВ** ± СОФ** или СОФ** + РБВ**, без цирроза печени в зависимости от генотипа (лекарственные средства представлены в алфавитном порядке)

	Pangenotypic treatment regimens Пангенотипные схемы лечения			Genotype-specific treatment regimens Генотип-специфичные схемы лечения		
ГТ GT	VEL+ SOF** ВЕЛ+ СОФ**	GLE+ PIB** ГЛЕ+ ПИБ**	DAC**+ SOF** ДАК**+ СОФ**	GRA+ ELB** ГРА+ ЭЛБ**	DSV; OBV+PTV/r** ДСВ; ОБВ+ПТВ/р**	LED+SOF ЛЕД+СОФ
1a	12 weeks 12 нед.	8 weeks 8 нед.	12 weeks 12 нед.	12/16 week [a] 12/16 нед.[a]	12 weeks + RBV** 12 нед.+ РБВ**	12 weeks 12 нед.
1b				12 weeks 12 нед.	12 weeks 12 нед.	
2				–	–	–
3		16 weeks 16 нед.		–	–	24 weeks + RBV** 24 нед. + РБВ**
4		8 weeks 8 нед.		12/16 week [a] 12/16 нед.[a]	–	12 weeks 12 нед.

Note:

VEL+SOF** — velpatasvir + sofosbuvir** (100/400 mg) 1 tab./day;

GLE+PIB** — glecaprevir + pibrentasvir** (3 tab. simultaneously, 100/40 mg each) per day;

DAC**+SOF** — daclatasvir** 60 mg 1 tab. 1 p/d + sofosbuvir** 400 mg 1 tab. per day;

GRA+ELB** — grazoprevir + elbasvir** 100/50 mg 1 tab. per day;

DSV; OBV+PTV/r** — dasabuvir (1 tab. 250 mg 2 times per day); ombitasvir + paritaprevir + ritonavir** (2 tab. simultaneously per day, 12.5/75/50 mg each);

LED+SOF — ledipasvir + sofosbuvir 90/400 mg 1 tab. per day;

a — if the HCV RNA level ≤ 800,000 U/ml, the treatment period is 12 weeks; 16-week course with RBV** should be considered for the HCV RNA level > 800,000 U/mL and/or NS5A polymorphisms;

Примечание:

ВЕЛ+СОФ** — велпатасвир + софосбувир** (100/400 мг) 1 таб. 1 р/д;

ГЛЕ+ПИБ** — глекапревир + пибрентасвир** (3 таб. одновременно по 100/40 мг каждая) 1 р/д;

ДАК**+СОФ** — даклатасвир** 60 мг 1 таб. 1 р/д + софосбувир** 400 мг 1 таб. 1 р/д;

ГРА+ЭЛБ** — гразопревир + элбасвир** 100/50 мг 1 таб. 1 р/д;

ДСВ; ОБВ+ПТВ/р** — дасабувир (1 таб. по 250 мг 2 р/д); омбитасвир + паритапревир + ритонавир** (2 таб. одновременно 1 р/д по 12,5/75/50 мг каждая);

ЛЕД+СОФ — ледипасвир + софосбувир 90/400 мг 1 таб. 1 р/д;

а — при ВН не более 800 000 МЕ/мл срок лечения 12 недель; 16-недельный курс совместно с РБВ** следует рассмотреть при ВН ВГС > 800 000 МЕ/мл и/или при наличии полиморфизмов NS5A.

All the regimens for the treatment of patients with HCV infection are also summarized in Appendix A3.

3.3. Treatment control

• All patients are recommended to assess the presence of HCV RNA (qualitative methods) 12 weeks after the end of treatment. It is recommended methods with high sensitivity (≤15 IU/ml) [46–48, 128]. The absence of HCV RNA 12 weeks after the end of the treatment means a cure for HCV infection. On the contrary, a positive HCV RNA result at this time indicates the failure of the treatment.

Grade of evidence C
(level of evidence 4)

• When using RBV** it is recommended to perform complete blood count every 2–4 weeks, and if the hemoglobin level decreases by ≥ 10 g/l from the initial, the dose of the drug is recommended to be reduced by 200 mg/day; if the hemoglobin level is < 85 g/l, RIB** is recommended to be cancelled [129–134].

Grade of evidence C
(level of evidence 5)

*Comments: Most modern DAA are well tolerated, but in some cases it is necessary to add RBV** (for some regimens, especially for patients with cirrhosis) that is a drug with main*

Table 5. Treatment of patients with HCV infection and compensated cirrhosis who did not respond to therapy PegIFN** + RBV** ± SOF** or SOF** + RBV** depending on the genotype
Таблица 5. Схемы ПВТ ХВГС для пациентов, не ответивших на предшествующую терапию ПегИФН** + РБВ** ± СОФ** или СОФ** + РБВ**, с компенсированным циррозом печени в зависимости от генотипа (лекарственные средства представлены в алфавитном порядке)

	Pangenotypic treatment regimens Пангенотипные схемы лечения			Genotype-specific treatment regimens Генотип-специфичные схемы лечения		
	VEL+SOF** ВЕЛ+ СОФ**	GLE+PIB** ГЛЕ+ ПИБ**	DAC**+SOF** ДАК**+СОФ**	GRA+ELB** ГРА+ЭЛБ**	DSV; OBV+ PTV/r** ДСВ; ОБВ+ ПТВ/р**	LED+SOF ЛЕД+СОФ
1a	12 weeks[b] 12 нед.[6]	12 weeks 12 нед.	12 weeks 12 нед.	12/16 weeks[a] 12/16 нед.[a]	24 weeks + RBV** 24 нед.+ РБВ**	12 weeks with RBV** 12 нед. + РБВ** 24 weeks without RBV** 24 нед. без РБВ**
1b				12 weeks 12 нед.	12 weeks 12 нед.	
2				–	–	–
3		16 weeks 16 нед.	24 weeks ± RBV** 24 нед. ± РБВ**	–	–	24 weeks + RBV**[c] 24 нед. + РБВ**[в]
4		12 weeks 12 нед.	12 weeks 12 нед.	12 weeks[a] 12 нед.[a]	–	12 weeks with RBV** 12 нед. + РБВ** 24 weeks without RBV** 24 нед. без РБВ**

Note:
VEL+SOF ** — velpatasvir + sofosbuvir** (100/400 mg) 1 tab./day;
GLE+PIB** — glecaprevir + pibrentasvir** (3 tab. simultaneously, 100/40 mg each) per aday;
DAC**+SOF** — daclatasvir** 60 mg 1 tab. 1 p/d + sofosbuvir** 400 mg 1 tab. per day;
GRA+ELB** — grazoprevir + elbasvir** 100/50 mg 1 tab. per day;
DSV; OBV+PTV/r** — dasabuvir (1 tab. 250 mg 2 times per a day); ombitasvir + paritaprevir + ritonavir** (2 tab. simultaneously per day, 12.5/75/50 mg each);
LED+SOF — ledipasvir + sofosbuvir 90/400 mg 1 tab. per day;
a — if the HCV RNA level ≤ 800,000 U/ml, the treatment period is 12 weeks; 16-week course with RBV** should be considered for the HCV RNA level > 800,000 U/mL and/or NS5A polymorphisms;
b — the addition of RBV** may be considered for genotype 3;
c — in a case of unavailability of other treatment regimens.
Примечание:
ВЕЛ+СОФ** — велпатасвир + софосбувир** (100/400 мг) 1 таб. 1 р/д;
ГЛЕ+ПИБ** — глекапревир + пибрентасвир** (3 таб. одновременно по 100/40 мг каждая) 1 р/д;
ДАК**+СОФ** — даклатасвир** 60 мг 1 таб. 1 р/д + софосбувир** 400 мг 1 таб. 1 р/д;
ГРА+ЭЛБ** — гразопревир + элбасвир** 100/50 мг 1 таб. 1 р/д;
ДСВ; ОБВ+ПТВ/р** — дасабувир (1 таб. по 250 мг 2 р/д); омбитасвир + паритапревир + ритонавир** (2 таб. одновременно 1 р/д по 12,5/75/50 мг каждая);
ЛЕД+СОФ — ледипасвир + софосбувир 90/400 мг 1 таб. 1 р/д;
а — при ВН не более 800 000 МЕ/мл срок лечения 12 недель; 16-недельный курс совместно с РБВ** следует рассмотреть при ВН ВГС > 800 000 МЕ/мл и/или при наличии полиморфизмов NS5A;
б — для ГТ 3 можно рассмотреть добавление РБВ**;
в — в случае недоступности иных схем лечения.

*side effect as nonimmune hemolysis. Therefore, when using RBV**, complete blood count should be monitored and, if necessary, correction of therapy should be carried out.*

• According to the decision of the attending physician, regardless of the conditions of medical care, it is recommended to consider the use of telemedicine technologies to monitor the DAA therapy (including assessing the effectiveness and safety) of adult patients with HCV infection [135, 136].

Grade of evidence C
(level of evidence 3)

3.4. Retreatment of DAA failures

In most cases (95–100 %), the use of DAAs leads to SVR, but in rare cases it is not possible to achieve SVR.

• With DAA failure, it is recommended to use a scheme with other drugs, as well as a combination of three drugs of different mechanism of action

(a drug that inhibits NS3/NS4A + a drug that inhibits NS5A + a drug that inhibits NS5B) without RBV** or with the addition of it. It is recommended to assess the presence of HCV mutations associated with resistance to various DAA for the selection of a new scheme if this tests is available [71–76, 137, 138].

Grade of evidence C
(level of evidence 4)

Comments:

• Velpatasvir + sofosbuvir** in dose of 100/400 mg per a day for 12 weeks is recommended for patients with HCV infection (genotypes 1–6) without cirrhosis or with compensated cirrhosis after the failure in therapy with inhibitors of NS3/4A ± inhibitors of NS5B;

• Velpatasvir + sofosbuvir in dose of 100/400 mg per day in combination with RBV** (600–1200 mg/day) for 12 weeks is recommended for HCV infection (genotypes 1–6) patients with decompensated cirrhosis after the failure in therapy with inhibitors of NS3/4A ± inhibitors of NS5B;

• Velpatasvir + sofosbuvir** in dose of 100/400 mg per day in combination with RBV** (600–1200 mg/day) for 24 weeks is recommended for HCV infection (genotypes 1–6) patients without cirrhosis or with compensated or decompensated cirrhosis after the failure in therapy with inhibitors of NS5A;

• Glecaprevir + pibrentasvir** (300/120 mg per a day) for 12 week is recommended for HCV infection (genotype 1) patients without cirrhosis or with compensated cirrhosis after the failure in therapy with inhibitors of NS3/4A without inhibitor of NS5A;

• Glecaprevir + pibrentasvir** (300/120 mg per a day) for 16 week is recommended for HCV infection (genotype 1) patients without cirrhosis or with compensated cirrhosis after the failure in therapy with inhibitors of NS5A without inhibitor of NS3/4A;

• Patients with HCV infection (genotypes 1–6) without cirrhosis or with compensated cirrhosis after the failure in therapy combined inhibitors of NS3/4A with inhibitors of NS5B can be considered for the use glecaprevir + pibrentasvir** (300/120 mg per day) in combination with sofosbuvir** (400 mg per day) ± RBV * * (1000–1200 mg/day) for 12–24 weeks according to the decision of the medical commission. The duration of the course is determined individually and depends on the stage of liver fibrosis, the presence of HCV variants resistant to DAA, and other factors.

3.5. Pathogenetic therapy

There is no pathogenetic therapy for patients with HCV infection.

3.6. Symptomatic therapy

There is no symptomatic therapy for patients with HCV infection.

3.7. Surgical treatment

• Liver transplantation is recommended if there are persistent signs of liver function decompensation in patients with cirrhosis [139–141].

Grade of evidence C
(level of evidence 4)

Comment: additional examination is carried out in accordance with the protocol for managing patients waiting liver transplantation.

• Patients with cirrhosis are recommended to perform endoscopic ligation or sclerotherapy of the esophageal and stomach varices to prevent bleeding or stop it [142–146].

Grade of evidence C
(level of evidence 4)

• Laparocentesis is recommended for patients with cirrhosis in the presence of refractory ascites for its relief [147].

Grade of evidence C
(level of evidence 5)

• It is recommended to perform transjugular intrahepatic portosystemic bypass surgery in patients with severe portal hypertension [147].

Grade of evidence C
(level of evidence 5)

3.8. Extrahepatic manifestations of HCV infection

• Patients with extrahepatic immunologically determined manifestations of HCV infection are recommended to be treated according to the schemes described above [23, 148–150].

Grade of evidence C
(level of evidence 5)

Comments: HCV infection can be manifested by extrahepatic immunologically determined disorders (cryoglobulinemic vasculitis, including Raynaud's syndrome, interstitial lung diseases, glomerulonephritis, Sjogren's syndrome, arthritis and others), as well as non-Hodgkin B-cell lymphomas. In all cases, the treatment should be prescribed according to the schemes described above. Early start of the antiviral treatment significantly reduces the risk of developing these manifestations.

3.9. Co-infection

3.9.1. HCV/HIV co-infection

Patients with HCV/HIV co-infection belong to the group requiring urgent DAA therapy [1, 69]. The course of HCV infection in HIV-infected patients depends on the severity of HIV-related immunodeficiency. The risk of severe liver damage is especially high with a decrease in CD4

lymphocytes of less than 200/ul. The progression of liver damage is due to an increase in the blood HCV level (2–8 times) in severe immunodeficiency. HCV/HIV co-infection leads to an increase in the incidence of complications, as well as mortality associated with these diseases. Antiretroviral therapy in HCV/HIV co-infected patients is associated with an increased risk of impaired liver function due to liver hepatotoxicity [151, 152].

· For the treatment of HCV infection in patients co-infected with HIV, it is recommended to use the same DAA regimens as for the treatment of HCV monoinfection [153–158].

Grade of evidence C
(level of evidence 4).

Comments: All DAA schemes require consideration of drug-drug interactions. One convenient way to assess drug-drug interactions is to use the Liverpool Table of Drug Interactions on the Internet Resource (http://www.hep-druginteractions.org).

3.9.2. HCV/HBV co-infection

Patients with HCV and hepatitis B virus (HBV) co-infection required immediate treatment of HBV infection [1, 69]. Co-infection with HCV/HBV accelerates the progression of the disease and increases the risk of developing HCC [159, 160].

· All patients with HCV infection are encouraged to be tested for past or ongoing HBV infection (for HBsAg, anti-HBs, anti-HBc) [161–164].

Grade of evidence C
(level of evidence 4)

· Patients with HCV/HBV co-infection are recommended to use anti-HBV nucleosides and nucleotides (not reverse transcriptase inhibitors) for the entire duration of HCV infection therapy, as well as for 12 weeks after its successful completion to prevent reactivation of HBV infection [163].

Grade of evidence A
(level of evidence 2)

Comments: Since HCV tends to suppress HBV replication, elimination of the first virus may lead to reactivation of the second. Therefore, in the treatment of HCV infection, biomarkers of HBV activity should be carefully monitored, and if they increase, HBV infection should be treated. This therapy can also be prescribed for prophylactic purposes for the duration of treatment of HCV infection and further within 12 weeks after its successful completion.

· Patients with HCV infection and anti-HBc (in the absence of HBsAg and anti-HBs) during HCV infection therapy are recommended monthly ALT monitoring to rule out HBV reactivation [163].

Grade of evidence A
(level of evidence 2)

· For HCV/HBV co-infection, it is recommended to use the standard regimens described above for the treatment of HCV monoinfection [1, 159, 163–166].

Grade of evidence A
(level of evidence 2)

3.10. Patients with chronic kidney disease (CKD)

· The patients with CKD (including severe, with GFR < 30 ml/min/1.73 m^2) can use DAA that recommended for patients without CKD [167–176] (see subsection 3.2 and Appendix A3).

Grade of evidence A
(level of evidence 1)

*Comments: to date, enough clinical experience has been accumulated with the use of sofosbuvir** in patients with severe CKD [174–176], which allows us to recommend sofosbuvir**-containing HTP regimens to all such patients without the correction of the doses.*

· For HCV infection treatment in patients with severe CKD (with GFR < 30 ml/min/1.73 m^2), however, it is recommended, if possible, to give preference to regimens that do not contain sofosbuvir** [167–173]:

· Glecaprevir + pibrentasvir** for all HCV genotypes;

· Dasabuvir; ombitasvir + paritaprevir + ritonavir** for genotype 1;

· Elbasvir + grazoprevir** for genotype 1, 4;

Grade of evidence A
(level of evidence 2)

· Patients with decompensated cirrhosis (Class B or C according to Child – Pugh) and severe CKD (with GFR < 30 ml/min/1.73 m^2) are recommended to use the following DAA regimens for 24 weeks [174–178]:

· Velpatasvir + sofosbuvir** (for all genotypes);

Grade of evidence C
(level of evidence 4)

· Daclatasvir** 1 tab. (60 mg) per day + sofosbuvir ** 1 tab. (400 mg) per day (for all genotypes);

· Ledipasvir + sofosbuvir (for genotypes 1 and 4).

Grade of evidence A
(level of evidence 2)

3.11. Liver transplantation

3.11.1. Antiviral therapy for HCV infection in patients with decompensated cirrhosis awaiting liver transplantation

The objectives of the antiviral therapy for HCV infection in patients with decompensated cirrhosis awaiting liver transplantation are:

· Prevention of infection of the liver transplant;

• Improvement of liver function before transplantation;

• mprovement in liver function resulting in no need for transplantation.

Improvement in liver function is assessed with Child – Pugh (see Appendix D) and MELD (any Internet resource can be used to calculate this index, for example, https://www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis) scales. Improvement in MELD score is observed in 60 % of patients with decompensated cirrhosis who complete the DAA course. This improvement is more likely and the more pronounced the lower the score MELD before starting therapy.

Up to 25–30 % of patients with decompensated cirrhosis can have a persistent improvement in liver function which allows to remove the patient from the liver transplantation waiting list. The survival rate of such patients for 3 years is not lower than in the group of liver recipients comparable to the initial MELD [139, 140, 179–183].

• It is recommended to prescribe DAA therapy to patients with decompensated cirrhosis (Child – Pugh B or C Class) due to HCV infection without HCC awaiting liver transplantation, if their MELD score is < 20. The DAA therapy is recommended to start as soon as possible, to complete the course and assess the response before transplantation [184, 185].

Grade of evidence B
(level of evidence 1)

Comments: In HTP patients with decompensated (Child – Pugh B or C) cirrhosis NS3/4 inhibitors is contraindicated.

• Patients with decompensated (Child – Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score > 20 should be transplanted first, without antiviral treatment, and HCV infection should be treated after liver transplantation [184, 185].

Grade of Recommendations B
(level of evidence 1)

• If the waiting time on the transplant list exceeds 6 months, patients with decompensated (Child – Pugh B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score > 20 should be treated before transplantation [184, 185].

Grade of Recommendations B
(level of evidence 1)

3.11.2. Treatment of hepatitis C in liver transplant recipients

• After liver transplantation HCV RNA positive patients should be treated depending on tolerance [186, 187].

Grade of Recommendations A
(Level of evidence 1)

Comments: The SVR12 in compensated liver transplant was 95 %. SVR is associated with slowing the progression of fibrosis and improving the survival of the graft and recipients.

3.12. Pregnant women

Women chronically infected with HCV can have an uneventful pregnancy without worsening of liver disease or other adverse effects on the mother or fetus. Serum ALT decreases in the first and third trimesters of pregnancy and increases after childbirth. HCV RNA levels rise up in the first and third trimesters and return to baseline postpartum, possibly related to the immune suppressive state during pregnancy [188, 189]. Transmission of HCV from the mother to the newborn occurs in 5 % to 15 % [190, 191]. There is no conclusive evidence of the negative effects of HCV on fetal development and pregnancy outcome. There are few reports of the effect of liver cirrhosis on pregnancy and outcome. For example, pregnant women with liver cirrhosis appear to have increased risk of adverse events for the mother (e.g., preeclampsia, hemorrhagic complications, and death) and for the fetus (e.g., preterm birth, low birth weight, and neonatal death). Women with liver cirrhosis caused by HCV infection should be informed of possible complications [192, 193].

• HCV treatment is recommended before planning a pregnancy to reduce the risk of HCV transmission [194].

Grade of Recommendations C
(level of evidence 5)

• HCV screening (anti-HCV IgG and anti-HCV IgM) is recommended in I and III trimesters of pregnancy [195].

Grade of Recommendations C
(level of evidence 5)

• HCV treatment during pregnancy is not recommended in the absence of safety and efficacy data of DAAs [196, 197].

Grade of Recommendations C
(level of evidence 4)

*Comments: Currently there are no large-scale published data on the safety and efficacy of HCV DAAs in pregnant women and none are licensed for use in pregnancy. Special studies of SOF** and LED+SOF treatment during pregnancy have demonstrated good fetal safety. Currently there is no data of pangenotypic regimens in pregnancy.*

• Women receiving HCV treatment with RBV** are not recommended to become pregnant during therapy course and at least 6 months after [198, 199].

Grade of Recommendations C
(level of evidence 4)

• Men receiving HCV treatment with RBV** are not recommended to get their sexual partners become pregnant while taking antiviral therapy and for at least 6 months after [198, 199].

Grade of Recommendations C
(level of evidence 4)

*Comments: RBV** has a teratogenic effects. It should not be administered to pregnant women or women of childbearing age who may become pregnant during treatment with RBV** or within 6 months of discontinuation of RBV**. RBV** can also cause birth defects in the fetus if a man has received RBV**, when a woman got pregnant by him. Thus, to avoid pregnancy during treatment with RBV** and for at least 6 months after, it is essential for individuals to use at least 2 forms of effective contraception. The consulting physician should document a discussion of the potential teratogenic effects of RBV** in the patient's medical record.*

• Breastfeeding is not contraindicated in women with HCV, except in the case of bleeding or cracked nipples for which specialist advice should be sought [200, 201].

Grade of Recommendations C
(level of evidence 4)

Comments: Breastfeeding is not associated with a risk for mother-to-child HCV transmission, as the incidence of infection of children according to studies is comparable in the breastfeeding and formula-fed groups. However, in the case of nipple damage and bleeding, there is a risk of HCV transmission through the blood.

4. Medical rehabilitation and spa treatment, medical indications and contraindications to the use of medical rehabilitation methods, including those based on the use of natural therapeutic factors

For patients with HCV infection, specialized rehabilitation measures have not been developed.

5. Prevention and regular medical checkup, medical indications and contraindications to the use of prevention methods

5.1. Specific prophylaxis

Specific prophylaxis of HCV infection is not currently developed.

• Patients with HCV infection should be vaccinated against hepatitis A and B to prevent infection with these viruses [1, 202–205].

Grade of Recommendations C
(level of evidence 4)

5.2. Non-specific prophylaxis

• Active identification of sources of infection (examination of persons at increased risk of infection and / or having special epidemiological significance) is recommended for the timely treatment [31, 32].

Grade of Recommendations C
(level of evidence 5)

• Prevention of the artificial mechanism of transmission (blood transfusion only for vital indications, validity of invasive methods of examination, use of disposable instruments, strict adherence to the treatment regimens of medical instruments and equipment, use of protective equipment by health workers) is recommended to reduce the risk of spreading infection caused by HCV [206–208].

Grade of Recommendations A
(level of evidence 1)

• Treatment is recommended for all HCV patients to prevent the spread of infection [17, 32, 209].

Grade of Recommendations C
(level of evidence 5)

5.3. Regular medical checkup

• Patients with HCV infection who have been postponed treatment are recommended to perform medical checkup once a year with a comprehensive clinical, laboratory and instrumental examination for dynamic observation [54, 55, 57, 59–61, 66, 67] (see also subsections 2.3, 2.4):

• All patients with HCV infection — biochemical blood test, abdominal ultrasound, liver elastometry (if it is not available, non-commercial calculation indicators based on the results of laboratory examination, for example APRI, FIB-4);

• All patients with HCV cirrhosis clinical blood test, prothrombin (thromboplastin) time, esophagogastroduodenoscopy.

Grade of Recommendations C
(level of evidence 4)

• Regular medical checkup is not recommended for patients with indications for the immediate onset of HCV treatment [1, 69] (see subsection 3.1).

Grade of Recommendations C
(level of evidence 5)

• Regular medical checkup is not recommended for patients without liver fibrosis, with mild and moderate liver fibrosis (METAVIR F0-F2) after reaching SVR12 [46–48] (see subsection 2.3).

Grade of Recommendations C
(level of evidence 5)

Comment: Patients with anti-HCV who do not have HCV RNA after antiviral treatment for 12 weeks are considered cured of CHC and should be excluded from follow-up.

• Follow-up is recommended for patients with severe liver fibrosis (F3–F4) who have received antiviral therapy, even after reaching SVR12 due to the continuing risk of developing HCC (control of blood AFP and ultrasound every six months) [44, 45, 53] (see subsections 2.3, 2.4).

Grade of Recommendations A (level of evidence 1)

6. Organization of medical care

Medical care is provided in the form of:
• Urgent medical care;
• Emergency medical care;
• Routine medical care.

Conditions of medical services

Medical care is provided in the form of:
• primary health care;
• ambulance, including specialized ambulance, medical care;
• specialized, including high-tech, medical care.

Medical care for adult for HCV patients can be provided in the following conditions:
• outpatient (in conditions that do not provide for round-the-clock medical supervision and treatment);
• inpatient (in conditions that provide for medical supervision and treatment in the daytime, do not require round-the-clock medical supervision and treatment);

stationary (in conditions that provide round-the-clock medical supervision and treatment).

Primary health care for patients is provided on an outpatient basis and in a day hospital setting.

Primary pre-medical health care on an outpatient basis is carried out in paramedic and obstetric stations.

Primary medical care is carried out by a district general practitioner, a general practitioner (family doctor) on an outpatient basis.

Primary specialized health care is carried out by an infectious disease doctor or gastroenterologist of a medical organization that provides medical care to patients on an outpatient basis.

Specialized, including high-tech, medical care is provided in a hospital setting by infectious disease doctors and other specialist doctors and includes prevention, diagnosis, treatment of diseases and conditions requiring the use of special methods and complex medical technologies, as well as medical rehabilitation.

Treatment of patients is carried out in a round-the-clock or day hospital in the direction of a district general practitioner, a general practitioner (family doctor), an infectious disease doctor, a gastroenterologist, medical workers who have identified HCV infection.

Patients with HCV infection should be monitored until SVR12 is reached, and in the presence of liver fibrosis F3–F4 by METAVIR for life.

Indication for emergency hospitalization is the development of acute liver failure, including hepatic encephalopathy and acute liver failure against the background of chronic.

Medical care for HCV infection patients is provided in accordance with the approved standard of specialized medical care.

7. Additional information (including factors affecting the outcome of the disease)

None.

Criteria for assessing the quality of medical care
Критерии оценки качества медицинской помощи

№	Quality criteria Критерии качества	Done Yes/No Сделано Да/нет
	Stage of diagnosis Этап постановки диагноза	
1.	HCV antibodies M and G (anti-HCV IgG and anti-HCV IgM) detection in the blood Определение суммарных антител классов M и G (anti-HCV IgG и anti-HCV IgM) к вирусу гепатита С в крови	
2.	HCV RNA (Hepatitis C virus) detection in the blood by PCR, qualitative analysis or HCV Core antigen detection in the blood Определение РНК вируса гепатита С в крови методом ПЦР, качественное исследование или определение Core-антигена вируса гепатита С в крови	
3.	The HCV genotype identification if a genotype-specific therapy is planned Определение генотипа вируса гепатита С, в случае если планируется генотип-специфичная схема ПВТ	
4.	Complete blood count Общий развернутый (клинический) анализ крови	
5.	A biochemical blood test was performed with an assessment of ALT, AST, total bilirubin and its fractions (free and bound bilirubin), creatinine Анализ крови биохимический общетерапевтический с оценкой АЛТ, АСТ, общего билирубина и его фракций (свободный и связанный билирубин), креатинина	
6.	Prothrombin (thromboplastin) time detection in patients with liver cirrhosis Определение протромбинового (тромбопластинового) времени в крови или в плазме у пациентов с циррозом печени	
7.	AFP analysis in patients with severe liver fibrosis (F3–F4 according to METAVIR) Определение у пациентов с выраженным и тяжелым фиброзом печени (F3–F4 по METAVIR) уровня АФП	
8.	Abdominal US УЗИ органов брюшной полости (комплексное)	
9.	Liver fibrosis was evaluated (liver elastometry and/or calculated fibrosis indexes and/or liver biopsy) Оценка фиброза печени (эластометрия печени и/или расчетные индексы фиброза и/или биопсия печени)	
10.	Esophagogastroduodenoscopy (patients with cirrhosis) Эзофагогастродуоденоскопия (пациентам с ЦП)	
	Antiviral therapy stage Этап ПВТ	
1.	In the case of RBV** clinical blood test every 2–4 weeks of treatment Общий развернутый (клинический) анализ крови каждые 2–4 недели ПВТ в случае применения РБВ**	
2.	HCV RNA (Hepatitis C virus) detection in the blood by PCR was performed, a qualitative study initially and 12 weeks after the end of therapy Определение РНК вируса гепатита С в крови методом ПЦР, качественное исследование исходно и через 12 недель после окончания терапии	
	Stage of regular medical checkup Этап диспансерного наблюдения	
1.	AFP analysis in patients with severe and severe liver fibrosis (METAVIR F3-F 4) every six months Определение у пациентов с выраженным и тяжелым фиброзом печени (F3–F4 по METAVIR) определен уровень АФП 1 раз в полгода	
2.	Liver fibrosis evaluation once per year (liver elastometry and/or calculated fibrosis indexes and/or liver biopsy) Оценка фиброза печени 1 раз в год (эластометрия печени и/или расчетные индексы фиброза и/или биопсия печени)	
3.	Abdominal US in patients with severe liver fibrosis (METAVIR F3–F4) every six months УЗИ органов брюшной полости (комплексное) раз в полгода у пациентов с выраженным и тяжелым фиброзом печени (F3–F4 по METAVIR)	
4.	Esophagogastroduodenoscopy annually in patients with liver cirrhosis Эзофагогастродуоденоскопия 1 раз в год у пациентов с циррозом печени	

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Appendix A2. Methodology for the development of clinical guidelines

The proposed recommendations are intended to bring to practitioners modern ideas about the etiology and pathogenesis of HCV infection, as well as to familiarize them with the algorithms currently used for its diagnosis and treatment.

The target audience of these clinical recommendations:

1. Infectious disease doctors;
2. Gastroenterologists;
3. General practitioners (family doctors);
4. Internists.

Table P1. Level of Evidence for diagnostic methods (diagnostic interventions)
Таблица П1. Шкала оценки уровней достоверности доказательств (УДД) для методов диагностики (диагностических вмешательств)

Level УДД	Meaning Расшифровка
1	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality Систематические обзоры исследований с контролем референсным методом или систематический обзор рандомизированных клинических исследований с применением метаанализа
2	Individual reference control studies or separate randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis Отдельные исследования с контролем референсным методом или отдельные рандомизированные клинические исследования и систематические обзоры исследований любого дизайна, за исключением рандомизированных клинических исследований, с применением метаанализа
3	Studies without sequential control by the reference method or studies with a reference method that is not independent of the method under study or non-randomized comparative studies, including cohort studies Исследования без последовательного контроля референсным методом или исследования с референсным методом, не являющимся независимым от исследуемого метода, или нерандомизированные сравнительные исследования, в том числе когортные исследования
4	Non-comparative studies, description of the clinical case Не сравнительные исследования, описание клинического случая
5	There is only a justification for the mechanism of action or the opinion of experts Имеется лишь обоснование механизма действия или мнение экспертов

Table P2. Level of evidence indicating the classification of evidence
Таблица П2. Уровни достоверности доказательств с указанием использованной классификации уровней достоверности доказательств (УДД)

Level УДД	Meaning Расшифровка
1	Systematic review of randomized clinical trials using meta-analysis Систематический обзор рандомизированных клинических исследований с применением метаанализа
2	Individual randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis Отдельные рандомизированные клинические исследования и систематические обзоры исследований любого дизайна, за исключением рандомизированных клинических исследований, с применением метаанализа
3	Non-randomized comparative studies, including cohort studies Не рандомизированные сравнительные исследования, в том числе когортные исследования
4	Non-comparative studies, description of a clinical case or a series of cases, case-control study Не сравнительные исследования, описание клинического случая или серии случаев, исследование «случай — контроль»
5	There is only a justification for the mechanism of action of the intervention (preclinical studies) or expert opinion Имеется лишь обоснование механизма действия вмешательства (доклинические исследования) или мнение эксперта

Table P3. Grade of Recommendations
Таблица П3. Уровни убедительности рекомендаций (УУР) с указанием использованной классификации уровней убедительности рекомендаций

Level УУР	Meaning Расшифровка
A	Strong recommendation (all outcomes considered are important, all studies are of high or satisfactory methodological quality, their conclusions on outcomes of interest are consistent) Сильная рекомендация (все рассматриваемые критерии эффективности (исходы) являются важными, все исследования имеют высокое или удовлетворительное методологическое качество, их выводы по интересующим исходам являются согласованными)
B	Conditional recommendation (not all outcomes considered are important, not all studies are of high or satisfactory methodological quality, and/or their conclusions on outcomes of interest are not consistent) Условная рекомендация (не все рассматриваемые критерии эффективности (исходы) являются важными, не все исследования имеют высокое или удовлетворительное методологическое качество и/или их выводы по интересующим исходам не являются согласованными)
C	Weak recommendation (lack of evidence of good quality (all outcomes considered are unimportant, all studies have low methodological quality and their conclusions on outcomes of interest are not consistent) Слабая рекомендация (отсутствие доказательств надлежащего качества) (все рассматриваемые критерии эффективности (исходы) являются неважными, все исследования имеют низкое методологическое качество и их выводы по интересующим исходам не являются согласованными)

Procedure for updating clinical guidelines

The mechanism for updating clinical guidelines provides for their systematic updating — at least once every three years, as well as when new data appear from the standpoint of evidence-based medicine on the diagnosis, treatment, prevention and rehabilitation of specific diseases, the presence of reasonable additions and / or comments to previously approved clinical recommendations, but not more than 1 time in 6 months.

Appendix A3. References

These clinical guidelines are developed taking into account the following regulatory and legal documents:

1. Order of the Ministry of Health and Social Development of the Russian Federation of January 31, 2012 No. 69n "On Approval of the Procedure for Providing Medical Care to Adult Patients with Infectious Diseases";
2. Order of the Ministry of Health and Social Development of the Russian Federation dated 02.06.2010 No. 415n "On Approval of the Procedure for Providing Medical Care to the Population in Diseases of the Gastroenterological Profile";
3. 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".

Schemes of antiviral therapy of chronic viral hepatitis C Depending on the genotype of the virus, therapy experence and the presence of cirrhosis of the liver (the names of medicines are listed in alphabetical order)

Patients with HCV HT 1
Scheme 1 **Velpatasvir + sofosbuvir**** VEL+SOFA** 1 tab. (100/400 mg) once daily ***12 weeks*** for patients without LC or with compensated LC, including those previously treated with PegIFN** + RBV** ± SOF** and/or NS3/4A inhibitors, and patients with recurrence of HCV after liver and solid organ transplantation. ***24 weeks — plus RBV**** 1000 or 1200 mg at a weight of < 75 kg or ≥ 75 kg, respectively, for patients without LC or with compensated LC, previously treated with NS5A inhibitors, including patients with relapse of HCV after liver and solid organ transplantation.
Scheme 2 **Glecaprevir + pibrentasvir**** GLE+PIB** (100/40 mg) 3 tab. simultaneously once daily ***8 weeks*** — for treatment-naïve patients without LC or with LC; for patients without LC who have not responded to previous therapy PegIFN** + RBV** ± SOF** or SOF** + RBV**; ***12 weeks*** for patients with LC who did not respond to previous therapy with PegIFN** + RBV** ± SOF** or SOF** + RBV**; for patients without LC or with LC with or without previous therapy with NS3 / 4A inhibitors; for patients with relapse of HCV after liver or kidney transplantation; 16 weeks for patients without LC or with LC with or without previous therapy with NS3/4A inhibitors, including patients with recurrence of HCV after liver or kidney transplantation.
Scheme 3 **Grazoprevir + elbasvir**** GRA+ELB** (100/50 mg) 1 tab. once daily. ***8 weeks*** — for treatment-naïve patients with subtype 1b, without severe liver fibrosis (F0—F2); ***12 weeks*** for patients with subtypes 1a (with an initial HCV RNA concentration of less than 800,000 IU/mL) or 1b without LC or compensated LC; ***16 weeks with RBV**** for patients with subtype 1a at baseline HCV RNA concentrations greater than 800,000 IU/mL and/or NS 5A polymorphism.
Scheme 4 Daclatasvir** + narlaprevir** + ritonavir** 12 weeks DAK** 1 tab. (60 mg) once daily + NRV** 2 tab. (100 mg each) once daily + r** 2 tab. (50 mg each) once daily. For treatment-naïve patients with subtype 1b without LC.
Scheme 5 **Daclatasvir** + sofosbuvir** 12 weeks** DAK** 1 tab. (60 mg) once daily + SOFA** 1 tab. (400 mg) once daily ***12 weeks*** — for treatment-naïve patients without LC and with compensated LC, and with previous ineffectiveness of PegIFN therapy** + RBV** and / or NS3/4A inhibitors ± SOF **; ***12 weeks*** — plus RBV** 15 mg/kg/d for patients with relapse of infection after liver transplantation.
Scheme 6 **Dasabuvir; ombitasvir + paritaprevir + ritonavir**** DSV 1 tab. (250 mg) bid; OBV+PTV/r** 2 tablets. (12.5/75/50 mg) once daily. ***8 weeks*** — for treatment-naïve patients with subtype 1b and liver fibrosis F0—F2;

12 weeks — for treatment-naïve patients with subtype 1b with liver fibrosis F3–F4, for patients with previous PegIFN** therapy with fibrosis F0–F4; for patients with subtype 1a without LC plus RBV**;
24 weeks — plus RBV* for patients with subtype 1a, with LC (12-week therapy with RBV** can be considered in this category of patients, taking into account the experience of previous therapy).

Scheme 7
Ledipasvir + sofosbuvir
LED+SOFA 1 tab. (90/400 mg) once daily

8 weeks — for treatment-naïve patients without LC;
12 weeks — for patients without LC who have previously received treatment with PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors, including patients with relapse of HCV after liver and solid organ transplantation;
12 weeks — plus RBV* 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively;
For treatment-naïve patients with compensated LC or previous treatment with PegIFN** + RBV** ± SOF** and/or NS3/4A inhibitors, including recurrence of HCV after liver and solid organ transplantation;
24 weeks — for treatment-naïve patients with LC (including after transplantation — plus RBV**) or received treatment pegIFN** + RBV** and / or NS3/4A inhibitors, including recurrence of HCV after liver and solid organ transplantation.

Scheme 8
Narlaprevir + ritonavir** + sofosbuvir****
NRV** 2 tab. (100 mg each) once daily + r** 2 tab. (50 mg each) once daily + SOFA** 1 tab. (400 mg) once daily.

#8 weeks — for patients with mild fibrosis and HV less than 1,000,000 IU/ml, 8 weeks can be considered (by decision of the medical commission).
12 weeks — for treatment-naïve patients without LC (F0–F3).

Patients with HCV GT 2

Scheme 1
Velpatasvir + sofosbuvir**
VEL+SOFA** 1 tab. (100/400 mg) once daily.

12 weeks for patients without LC or with compensated LC, including those previously treated with PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors, and patients with recurrence of HCV after liver and solid organ transplantation.
24 weeks — plus RBV* 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively, for patients without LC or with compensated LC, previously treated with NS5A inhibitors, including patients with recurrence of HCV after liver and solid organ transplantation.

Scheme 2
Glecaprevir + pibrentasvir**
GLE+PIB (100/40 mg) 3 tab. simultaneously once daily.

8 weeks — for treatment-naïve patients without LC or with LC; for patients without CP who have not responded to previous therapy PegIFN** + RBV** ± SOF** or SOF** + RBV**;
12 weeks — for patients with LC who did not respond to previous therapy PegIFN** + RBV** ± SOF** or SOF** + RBV**; for patients with recurrence of HCV after liver or kidney transplantation.

Scheme 3
Daclatasvir + sofosbuvir** 12 weeks**
DAK** 1 tab. (60 mg) once daily + SOFA** 1 tab. (400 mg) once daily.

12 weeks — for treatment-naïve patients without LC and with compensated LC, or with previous ineffectiveness of PegIFN therapy** + RBV** and / or NS3/4A inhibitors ±SOF **;
12 weeks — plus RBV* 15 mg/kg/day for patients with recurrence of HCV after liver transplantation.

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Patients with HCV GT 3

Scheme 1
Velpatasvir + sofosbuvir**
VEL+SOFA** 1 tab. (100/400 mg) once daily.

12 weeks for patients without LC, including those previously treated with PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors, and patients with recurrence of HCV after liver and solid organ transplantation;
24 weeks — plus RBV* 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively, for patients without LC or with compensated LC, previously treated with NS5A inhibitors, including patients with recurrence of HCV after liver and solid organ transplantation.

Scheme 2
Glecaprevir + pibrentasvir**
GLE+PIB (100/40 mg) 3 tab. simultaneously once daily.

8 weeks — for treatment-naïve patients without LC or with LC;
16 weeks — for patients without LC or with LC who have previously received PegIFN** + RBV** ± SOF**, SOF** + RBV**; for patients with recurrence of HCV after liver or kidney transplant.

Scheme 3
Grazoprevir + elbasvir + sofosbuvir 12 weeks**
GRA+ELB** (100/50 mg) 1 tab. 1 once daily + SOFA** 1 tab. (400 mg) once daily.

For treatment-naïve patients without LC and with compensated LC.

Scheme 4
Daclatasvir + sofosbuvir****
DAK** 1 tab. (60 mg) once daily + SOFA** 1 tab. (400 mg) once daily.

12 weeks — for treatment-naïve patients without LC, or with previous ineffectiveness of Therapy with PegIFN** + RBV** and / or NS3/4A inhibitors ± SOF**;
12 weeks — plus RBB* 15 mg/kg/day
for patients with recurrent infection after liver transplantation;
24 weeks — with or without RBB* 15 mg/kg/day
For treatment-naïve patients with compensated cirrhosis, or with previous ineffectiveness of PegIFN therapy** + RBV** ± SOF** and / or NS3/4A inhibitors.

Scheme 5
Ledipasvir + sofosbuvir + ribavirin 24 weeks**
LED+SOFA 1 tab. (90/400 mg) 1 once daily + RBV** 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively.For patients with compensated LC and/or previously treated with PegIFN** + RBV** ± SOF** and/or NS3/4A inhibitors.

Patients with HCV HT 4

Scheme 1
Velpatasvir + sofosbuvir**
VEL+SOFA** 1 tab. (100/400 mg) once daily.

12 weeks for patients without LC or with compensated LC, including those previously treated with PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors, and patients with recurrence of HCV after liver and solid organ transplantation;
24 weeks — plus RBV* 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively, for patients without LP or with compensated LC, previously treated with NS5A inhibitors, including patients with recurrence of HCV after liver and solid organ transplantation.

Scheme 2
Glecaprevir + pibrentasvir**
GLE+ PIB** (100/40 mg) 3 tab. simultaneously once daily.

8 weeks — for treatment-naïve patients without LC or with LC; for patients without LC who have not responded to previous therapy PegIFN** + RBV** ± SOF** or SOF** + RBV**;

12 weeks — for patients with LC who did not respond to previous therapy PegIFN** + RBV** ± SOF** or SOF** + RBV**; for patients with recurrence of HCV after liver or kidney transplantation.

Scheme 3
Grazoprevir + elbasvir**
GRA+ELB** (100/50 mg) 1 tab. once daily.

12 weeks — for patients with a baseline HCV RNA concentration of less than 800,000 IU/mL.
16 weeks in combination with RBV**, for patients with subtype 4 at baseline HCV RNA concentrations greater than 800,000 IU/mL.

Scheme 4
Daclatasvir + sofosbuvir****
DAK** 1 tab. (60 mg) once daily + SOFA** 1 tab. (400 mg) once daily.

12 weeks — for treatment-naïve patients without LC and with compensated LC, or with previous ineffectiveness of PegIFN therapy** + RBV** and /or NS3/4A inhibitors ± SOF**;
12 weeks — with the addition of RBV* 15 mg/kg/day for patients with recurrence of infection after liver transplantation.

Scheme 5
Ledipasvir + sofosbuvir
LED+SOFA 1 tab. (90/400 mg) once daily.

12 weeks for patients without LC, including those previously treated with PegIFN** + RBV** and/or NS3/4A inhibitors;
12 weeks — plus RBV* 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively;
For patients with compensated LC who have previously received treatment and have not previously received treatment PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors;
24 weeks — for treatment-naïve patients with compensated LC or who have previously received treatment with PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors.

Patients with decompensated LC

Scheme 1 (all GT)
Velpatasvir + sofosbuvir + ribavirin** 12 weeks**
VEL+SOFA** 1 tab. (100/400 mg) 1 once daily + RBV** 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively.

For patients with decompensated LC (Child – Pugh B or C), including treatment-experienced patients (PegIFN** + RBV** ± SOF** and / or NS3/4A inhibitors), and patients with recurrent HCV after liver and solid organ transplantation. In patients with decompensated (Child – Pugh C) cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance to a maximum of 1000/1200 mg (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively).
For treatment-experienced patients (NS5A inhibitors), the duration of treatment should be increased to 24 weeks.

Scheme 2 (for GT 1,2,3,4)
Daclatasvir + sofosbuvir** + ribavirin****
DAK** 1 tab. (60 mg) once daily + SOFA* 1 tab. (400 mg) once daily + RBV** 15 mg/kg/day.

12 weeks — for treatment-naïve and treatment-experienced patients (PegIFN therapy** + RBV** ± SOF** and / or NS3/4A inhibitors) Child – Pugh B cirrhosis;
24 weeks — for treatment-naïve and treatment-experienced patients (PegIFN therapy** + RBV** ± SOF** and / or NS3/4A inhibitors) with Child – Pugh C cirrhosis. For patients with intolerance to RBV**, a regimen without RBV** may be considered.

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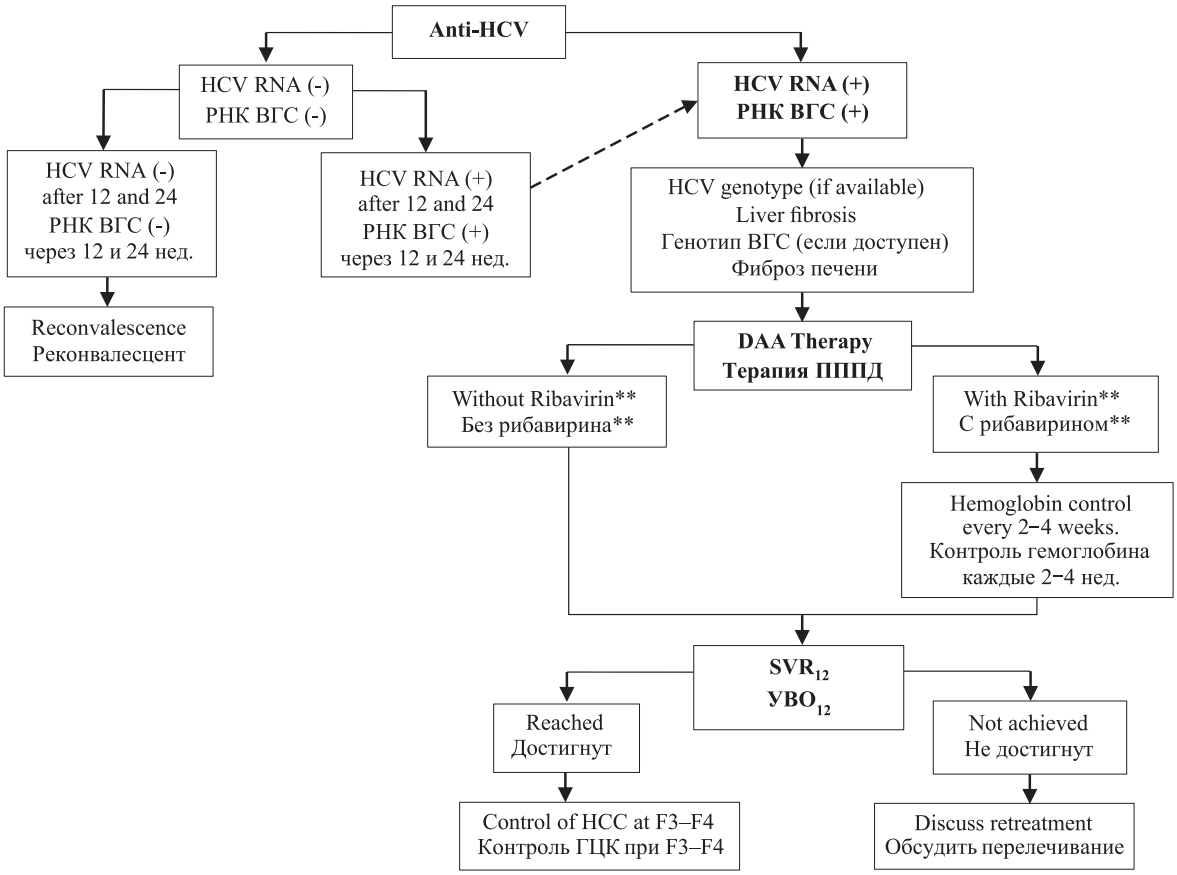
Scheme 3 (for GT 1.4-6)
Ledipasvir + sofosbuvir + ribavirin 12 weeks**
LED+SOFA 1 tab. (90/400 mg) once daily + RBV**1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively.

For treatment-naïve and treatment-experienced patients (PegIFN therapy** + RBV** ± SOF** and / or NS3/4A inhibitors) with decompensated cirrhosis. In patients with decompensated (Child – Pugh C) cirrhosis, prior to transplantation ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance to a maximum of 1000/1200 mg (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively).
If there is an intolerance to RBV**, the use of LED + SOF without RBV ** for 24 weeks may be considered.

Appendix B. The algorithm of the doctor's actions Diagnosis and treatment of HCV



Appendix C. Patient Information

Dear patient! You have hepatitis C. Modern medicines can completely cure this disease. This will prevent the development of complications such as cirrhosis and liver cancer. Usually, the disease proceeds without symptoms and is detected by a random examination. However, this does not mean that it should not be treated. The scope of therapy will be determined by your doctor. He/She will also determine the list of necessary studies and their periodicity. You should not cancel or replace medications yourself, even if you feel better or consider yourself a healthy person. If you have any questions, please contact your doctor.

Appendix D: Rating scales given in clinical guidelines Appendix D1. Assessment of the severity of liver cirrhosis on the Child – Pugh scale

Title in Russian: Assessment of the severity of liver cirrhosisr on the Child – Pugh scale
Source: Durand F., Valla D. Assessment of the prognosis of cirrhosis: Child – Pugh versus MELD. Journal of hepatology. 2005;42(1):S100–7.
Type: Rating Scale
Purpose: assessment of the severity of cirrhosis of the liver
Content:

Parameter Оцениваемые параметры	Numerical Score Число баллов в зависимости от значения параметра		
	1 point 1 балл	2 points 2 балла	3 points 3 балла
Ascites Асцит	None Отсутствует	Slight (easy to treat) Мягкий (легко поддается лечению)	Severe (poorly controlled) Напряженный (плохо контролируемый)
Total bilirubin, umol/L (mg/dL) Общий билирубин, мкмоль/л (мг/дл)	< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
Albumin, mg/l Альбумин крови, г/л	> 3.5	2.8–3.5	< 2.8
Hepatic encephalopathy Печеночная энцефалопатия	None Отсутствует	Slight/moderate I–II ст. (легкая. терапевтически контролируемая)	Moderate/severe III–IV ст. (тяжелая. плохо контролируемая)
PTI, % or PTV, sec or INR ПТИ, % или ПТВ, сек или МНО	> 60 or 1–4 or < 1.70 > 60 или 1–4 или < 1.70	40–60 or 4–6 or 1.71–2.20 40–60 или 4–6 или 1.71–2.20	< 40 or > 6 or > 2.20 < 40 или > 6 или > 2.20

Key (interpretation)
Points are set depending on the value of each of the parameters from 1 to 3, then they are summed up. The survival rate of the patients with CP depending on the points:

Child – Pugh Class Класс по Чайлду – Пью	Points Баллы	1-year survival rate, % Годичная выживаемость, %	2-years survival rate, % Двухлетняя выживаемость, %
A	5–6	100	85
B	7–9	81	57
C	10–15	45	35

Appendix D2. Calculation of the APRI fibrosis index

Title: Calculating the APRI Fibrosis Index
Source: Yen Y.H., et al. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PloS one. 2018;13(6):e0199760.
Type: Zip code
Contents: Calculated formula:
APRI = (AST/ULN AST) × 100 / platelets (10^9/L)
AST – the value of the patient's aspartate aminotransferase
ULN AST – the upper limit of the AST normal value
Platelets (109 / l) – the number of platelets of the patient in 1 liter of blood
Key (interpretation):

APRI Value Значение APRI	Conclusion Вывод	Rating scale Шкала оценки
> 2.0	F4	METAVIR
≥ 1.5	F3–F4	METAVIR
0.5–1.5	Guestionable result Сомнительный результат	
< 0.5	F0–F2	METAVIR

Appendix D3. Calculation of the fibrosis index FIB-4

Title: FiB-4 Fibrosis Index Calculation

Source: Yen Y.H., et al. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PloS one. 2018;13(6):e0199760.

Type: Index

Contents: Calculation formula:

FIB-4 = Age (years)) × AST/platelets (10^9/L) × √ALT

Age — age of the patient (years)

AST — the value of the patient's aspartate aminotransferase

Platelets (109 / l) — the number of platelets of the patient in 1 liter of blood

√ALT is the square root of the patient's ALT value

FIB-4 Value Значение FIB-4	Conclusion Вывод	Rating scale Шкала оценки
> 3.25	F3–F4	METAVIR
< 1.45	F0–F2	METAVIR
1.45–3.25	Guestionable result Сомнительный результат	

Appendix D4. Stages of liver fibrosis on the METAVIR scale

Title: METAVIR Scale

Source: Shiha G., Zalata K. Ishak versus METAVIR: terminology, convertibility and correlation with laboratory changes in chronic hepatitis C. Liver biopsy. 2011;10:155–70.

Type: Scale

Content and key (interpretation):

F0	No fibrosis Фиброз отсутствует
F1	Fibrosis expansion into some portal areas Звездчатое расширение портальных трактов без образования септ
F2	Fibrosis expansion in most portal areas, with occasional portal-to-portal bridging Расширение портальных трактов с единичными портопортальными септами
F3	Fibrosis expansion of portal areas with marked bridging, including portal-to-portal and portal-to-central bridging Многочисленные портоцентральные септы без цирроза
F4	Cirrhosis Цирроз

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