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KHARKOV NATIONAL MEDICAL UNIVERSITY

DEPARTMENT OF INTERNAL MEDICINE N3

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS
"Chronic hepatitis"

Kharkiv 2013

Module № 2 "Fundamentals of diagnosis, treatment and prevention of major diseases of the digestive system"

“Chronic hepatites (CH)”

Topicality

Despite significant advances in the diagnosis of diseases of the digestive system, the specific nosological diagnosis can't be made easily in some cases. This basically applies to diffuse chronic liver disease (DCLD) - chronic hepatitis (CH), occurring with relatively nonspecific clinical symptoms (discomfort in the right upper quadrant, fatigue, jaundice, hepatomegaly, biochemical changes, etc.). Often doctor has no opportunity to perform morphological study of the liver, ie the needle biopsy (PBI), therefore he has to formulate diagnosis empirically, which is not sufficient.

Learning Objectives:

1. To teach students to recognize the main symptoms and syndromes of CH;
2. To familiarize students with physical methods in CH;
3. To familiarize students with research methods used for the diagnosis of CH, indications and contraindications for their conduct, methods of execution, the diagnostic value of each of them;
4. To teach students to interpret the results of study;
5. To teach students how to recognize and diagnose complications of CH;
6. To teach students how to prescribe treatment for CH.

What should a student know?

1. Incidence of CH;
2. Etiological factors of CH;
3. Pathogenesis of CH;
4. Main clinical syndromes of CH;
5. General and alarm symptoms in CH;
6. Physical symptoms of CH;
7. Diagnosis of CH;
8. Morphological study of the liver (biopsy) in CH;
9. Instrumental methods of diagnosis of CH;
10. Differential diagnosis of CH;
11. Classification CH;
12. Complications of CH;
13. CH treatment (lifestyle modification, nutrition, drug therapy).

What students should be able to do?

1. To define main clinical and physical syndromes of CH;
2. To interpret the results of biochemical and immunoenzyme studies;
3. To interpret the data of liver biopsy;
4. To interpret the data of instrumental methods of liver examination;
5. To perform the differential diagnosis;
6. To prescribe treatment for patients with CH.

List of practical skills that students must learn:

1. Examination of the abdomen;
2. Superficial palpation of the abdomen;
3. Methodological deep sliding palpation of the abdomen after Obratzov-Strazhesko;
4. Examination of skin and mucosa;
5. Physical data of liver examination.

Topic content

Chronic hepatitis

Chronic inflammatory injury to the liver, persisting beyond 6 months, with preserved lobular structure of the liver.

Clinical presentation

The clinical presentation of chronic hepatitis depends on the activity of process and stage of disease, severity of hepatic and extrahepatic manifestations.

Asthenovegetative syndrome: weakness, severe fatigue, poor performance and mood, anxiety, depressive mood, hypochondria. These symptoms reflect deviations of all types of metabolism that accompany the disease. Significant weight loss is typical (5-10 kg).

Diarrheal syndrome - is an early sign of liver damage. Dryness and bitter taste in the mouth, nausea, vomiting, belching. The feeling of discomfort in the right upper quadrant, constant bloating, loss of appetite combined with intolerance to many foods. Constipation, especially marked in case of portal hypertension, unstable defecation.

Abdominal pain. Pain in the liver - a common symptom of the disease caused by the stretching of the fibrous membrane of the liver. The pain is constant, dull, moderate, slightly increases after exercise.

Cholestatic syndrome. Manifests as persistent or intermittent icteritiousness of skin, itching, dark urine, lightly coloured feces.

Vegetoasthenic syndrome - a psycho-emotional instability, insomnia, headache, false angina, headaches, fluctuating blood pressure, sweating.

Hemorrhagic syndrome - bleeding from the nose and gums, subcutaneous hemorrhage, menorrhagia, bloody vomiting, black coloring of feces.

Edematous-ascitic syndrome - fluid retention, increased size of the stomach, lower limbs swelling.

Encephalopathic syndrome - loss of memory, drowsiness, periodic disorientation in time and space, inappropriate behavior.

Febrile syndrome - occurs due to bacterial overgrowth with severe endogenous intoxication, periodic bacteremia.

Articular syndrome - joint pain (prolonged or intermittent), without deformation, usually accompanies active forms of hepatitis.

Physical data: greyish-pale skin is typical for patients with chronic liver disease. Often there is a local or diffuse hyperpigmentation of skin (melanoderma). Pallor develops due to posthemorrhagic anemia or hemolytic anemia that are possible in cirrhosis.

JAUNDICE. Early clinical signs of jaundice appear in case of hyperbilirubinemia over 30 mmol / l, jaundice becomes pronounced when the bilirubin level exceeds 120 mmol / l. Yellow tint first appears on the sclera and mucous membrane of soft palate. Sometimes icteric coloration is partial and is located in the nasolabial triangle, forehead, palms. In case of intense jaundice with high level of direct reacting bilirubin, color eventually becomes greenish-yellow due to oxidization of bilirubin into biliverdin.

SKIN EXCORIATIONS. Itching and excoriation traces on the skin are usually caused by accumulation of bile acids in the skin. Itching can develop in the absence of jaundice.

SPIDER ANGIOMAS. Telangiectasias consist of pulsating central part and thin vessels, which resemble the sunrays or spider. Dimensions of telangiectasia range from 1 mm to 1-2 cm. Large angiomas may pulsate, pulsation of small angiomas may be detected while pressing on the skin.

The most common spider angiomas are located in the neck, face, shoulders, back, wrists or on the mucosa of the palate and pharynx. These elements usually occur in patients with active processes in the liver - acute or chronic active hepatitis, cirrhosis; the proximate cause for their occurrence is hyperestrogenemia.

XANTHOMA AND XANTHELASMA. Xanthoma represents intradermal yellow plaques that form in case of marked dyslipidemia. They are not specific for liver disease and usually develop in patients with atherosclerosis, diabetes, and chronic cholestasis of different

etiology. May be localized on the hands, elbows, knees, feet, buttocks, arm pits, very often - on the eyelids (xanthelasma).

PETECHIAE, ECCHYMOSIS. Hemorrhages into the skin, dot hemorrhages and other symptoms of hemorrhagic syndrome are caused by decreased synthesis of coagulation factors, thrombocytopenia, acute vascular purpura. These are the signs of severe liver lesion. For chronic liver disease the petechial hemorrhage or microcirculatory type of bleeding is typical. They include painless superficial hemorrhages in the skin and mucous membranes, bleeding from the gums, nose, metrorrhagia. The reason for hypocoagulation is decreased synthesis of clotting factors in the liver and formation of abnormal clotting factors (dysfibrinogenemia).

Thrombohemorrhagic syndrome may be caused by consumption coagulopathy that accompanies DIC (disseminated intravascular clotting). The reason for occurrence of this syndrome is decreased function of reticuloendothelial system that normally removes components of the activated coagulation system and fibrinolysis. DIC in patients with cirrhosis manifests by reduced concentration of fibrinogen, decreased number of platelets and blood, lengthening of thrombin time.

LIVER PALMS. Palmar erythema is a symmetric splotchy red palms and soles, especially pronounced in the area of thenar and hypotenar. Spots become pale under the pressure and then quickly turn red again with the termination of pressure. The cause of erythema is arteriovenous anastomoses, which develop due to the high level of estrogen, they are typical for the active processes in the liver.

"RASPBERRY" TONGUE. "Cardinal tongue" is characterized by the absence, smoothening of papillae of the tongue to the degree of "patent" surface. The bright red color is caused by thinned mucosa, varicose vessels due to hyperestrogenemia.

MUSCLE ATROPHY. Muscle atrophy is caused by disorders of protein metabolism, hormonal imbalance.

Dupuytren's contracture is a marker of alcoholic liver disease.

OSTEOPATHY. There is thickening of the distal phalanges of the fingers ("drumsticks") because of severe dysproteinemia.

ENDOCRINE DISORDERS. Gynecomastia, feminizing type of body hair growth due to the significant increase in estrogen levels develop in patients with severe liver lesion. Possible changes include loss of pubic and armpit hair, testicular atrophy, hypertrophy of parotid salivary glands. The syndrome most often occurs in alcoholic hepatopathy.

SWELLING. Swelling of lower limbs, limfadenopathy in case of severe hypoalbuminemia.

HEPATOMEGALY. Enlargement of the liver is the hallmark of parenchyma lesion. Reduction of the liver size is rare and it happens in the later stages when cirrhosis develops. Hepatomegaly is caused by infiltration by immune cells in case of hepatitis; in case of cirrhosis hepatomegaly occurs as the result of development of sites of regeneration and fibrosis, cholestasis. Increased liver size is sometimes visible when looking at abdomen. It looks like a "tumor" in the right upper quadrant or epigastrium that moves with breathing, or as a deformity of the chest on the right side.

Percussion reveals increased liver size: vertical dimensions along parasternal, mid-clavicular and anterior axillary lines exceed 10-12 cm, 9-11 cm and 8-10 cm respectively. Liver increases not only down but also to the left - the left border of dull sound goes beyond left parasternal line. The progressive reduction in the size of liver dullness is a bad prognostic sign. Palpation of the liver can determine its topographic characteristics more accurately. Palpation during active phase of pathological process reveals liver tenderness, caused by stretching of its fibrous capsule. In healthy individuals liver edge is soft, even and smooth. Compaction of liver consistency always points to its destruction. Liver pathology is usually accompanied by compaction of liver, sharpening of its edge, uneven surface on palpation.

SPLENOMEGALY and HYPERSPLENISM syndrome. Splenomegaly can be determined by palpation and percussion of the spleen. However, it is not typical for most cases of hepatitis.

ADDITIONAL DIAGNOSTIC TESTS

CBC. Anemia can be found in 50-70% of patients with chronic liver diseases, especially in patients with cirrhosis. The mechanism of anemia development is complicated – hemolytic processes, hemorrhages, which are particularly severe in portal hypertension.

Severe and active chronic hepatitis may be accompanied by leukopenia. Acute alcoholic hepatitis is usually accompanied by leukocytosis, shift to the left and marked acceleration of ESR. Toxic leukocytosis appears in case of hepatic coma.

CLINICAL ANALYSIS OF URINE. "Urinary syndrome" is possible - microhematuria, moderate proteinuria caused by disorders of renal hemodynamics.

BIOCHEMICAL STUDY

SYNDROME of CYTOLYSIS

Accumulation of intracellular enzymes in the blood serum indicates necrotic processes in the body. Indicator enzymes of hepatocytes cytolysis are transaminases (AST, ALT), dehydrogenases (glutamatdehydrogenase GDG, laktatdehydrogenase-LDG), increased levels of iron and vitamin B-12 in serum. Release of enzymes from hepatocytes occurs either due to increased permeability of cell membranes, or by destruction of cells. Necrotized hepatocytes can no longer cause hiperaminotransferasemia. Activity of cytosolic enzymes (ALT, LDG) may be increased even in a relatively mild process. Activity of mitochondrial enzymes (AST, GDG) may be increased only in severe necrotic processes.

Cholestasis syndrome. Excretory enzymes (cholestasis indicators) are located on the plasma membrane of hepatocytes and in biliary cells of bile ducts. Increase of their activity in the blood is the result of enzyme induction (increased synthesis) and increased permeability of the membrane of hepatocytes. Obstruction of bile flow in intrahepatic or extrahepatic bile ducts is accompanied by selective stimulation of synthesis of excretory enzymes.

The indicators of cholestasis are the membrane-bound enzymes - alkaline phosphatase, gammaglobulintranspeptidase (GGTP) leucineaminopeptidase (LAP), 5-nucleotidases. Disorders of pigment metabolism are typical for CH – increase of conjugated (direct) bilirubin and general serum bilirubin. Cholestasis is accompanied by the accumulation of cholesterol in the blood serum.

SYNDROME OF IMMUNE INFLAMMATION. The level of total serum protein is elevated due to the accumulation of globulins, especially beta and gamma globulins. The sedimentary colloidal tests are positive - thymol, sublimate, formalin. The level of immunoglobulins A, F, G is increased.

SYNDROME OF SYNTHETIC LIVER FUNCTION DEFICIENCY. The reduction of synthetic liver function reveals itself through lowering of blood albumins that are formed only in the liver, decreased content of prothrombin complex proteins as well as lowering other enzymes of blood coagulation system. The acute decline in choline esterase activity may lead to reduction of esterified cholesterol in the blood serum.

SYNDROME OF HEPATIC HYPERAZOTEMIA. Increase of total nitrogen in serum and accumulation of aromatic amino acids (tyrosine, phenylalanine, tryptophan), phenols and indican.

IMMUNOLOGICAL DISORDERS. Changes of humoral immunity include the increase of immunoglobulins A, F, G content and the accumulation of serum circulating immune complexes (CIC). These changes prove the increased antibody producing activity of immune cells.

Serological markers of HBV infection:

- HBsAg – superficial antigen
- HBeAg – e core antigen
- HBcAg – c core antigen
- AntiHBc total – total antibodies to HBcAg
- Ig M anti HBc – antibodies of class M to core antigen
- HBV DNA

Serological markers of HDV infection:

- Ig M anti HDV – antibodies of class M to HDV
- Ig G anti HDV – antibodies of class G to HDV
- HDAg – antigen of HDV
- HDV RNA

Serological markers of HCV infection:

- Anti HCV Ig G – antibodies of class G to HCV
- Anti HCV core Ig M – antibodies of class M to core proteins of HCV
- Anti HCV core Ig G – antibodies of class G to core proteins of HCV
- HCV RNA

Chronic viral unspecified hepatitis is caused by viruses "neither A nor B". This diagnosis is made in cases of viral CH, when the patient's blood markers of viruses B, D, C are negative (viruses A and E cause only acute hepatitis). Diagnosis of unspecified viral CH is made when epidemiological, morphological, clinical and biochemical data suggest a viral etiology of CH, but markers of a specific viruses, as well as other reasons for CH are negative.

Diagnosis of autoimmune hepatitis is made according to the following criteria:

- The absence of a history of blood transfusions, intake of hepatotoxic drugs, alcohol abuse
- The absence of serum markers of active viral infection;
- T-globulin levels exceed normal more than 1.5 times;
- ANA or Anti-Smooth Muscle antibody positive, titer usually > 1:100
- A significant increase of AST, ALT activity and less pronounced increase of alkaline phosphatase (AP).

10% of patients with autoimmune hepatitis will have an antibody to Soluble Liver antigens (SLA). Other Antibodies: anti-DNA, ANCA, Anti-mitochondrial, Anti-Actin (AAA), cytoskeletal antibody, nuclear envelope proteins lamin A and C, plasma membrane sulfatides.

Drug-induced CH develops as the result of more or less chronic administration of hepatotoxic medications - tranquilizers, neuroleptics, anabolic steroids, tuberculostatic agents, antibiotics (especially tetracycline), propranolol, estrogen contraceptives, methotrexate, leuceran et al.

Cryptogenic CH is liver disease with characteristic morphological changes of CH and absence of viral, autoimmune and drug etiology.

Lack of CH of alcoholic etiology in modern international classification is very discussable.

According to the International Work Group of Experts, supported by the World Congress of Gastroenterology (1994), CH also includes such disease as:

- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Wilson's disease,
- Liver disease, which is caused by deficiency of alpha-antitrypsin.

The degree of activity of CH is determined by the severity of cytolysis and inflammatory changes (infiltration) in the liver.

Instrumental methods of liver examination:

Ultrasound: defines increase of liver size and changes of its texture, helps to access the gallbladder and intrahepatic bile ducts, defines the size of a spleen, and determines the presence of collateral vessels and portal venous flow.

CT and MRI are less helpful unless a mass or other abnormality is found by ultrasound

Liver biopsy: Hepatic histologic characteristics in patients with chronic hepatitis include: spotty hepatocellular necrosis, chronic inflammatory cell infiltration in portal areas, variable degrees of fibrosis. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis. In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis.

In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. In patients with histologic but not serologic criteria for chronic autoimmune hepatitis, variant autoimmune hepatitis is diagnosed; many have overlap syndromes.

Hepatic histologic analysis is useful for grading the severity of necroinflammation and for staging the degree of fibrosis in chronic hepatitis, helps to exclude other diagnoses.

DIFFERENTIAL DIAGNOSIS OF CHRONIC HEPATITIS

Differential diagnosis is made with a number of diseases:

1. Right-side heart failure.
2. Chronic cholangitis.
3. Idiopathic amyloidosis.
4. Amebiasis.
5. Echinococcosis of liver.
7. Cysts of the liver.
8. Tumors of the liver.
9. Metastatic liver damage.

CLASSIFICATION OF CH (International Congress of Gastroenterology, Los Angeles, 1994)

1. By etiology:
 - chronic viral hepatitis B
 - chronic viral hepatitis C
 - chronic viral hepatitis D
 - chronic viral hepatitis of other origin
 - autoimmune hepatitis
 - toxic hepatitis
 - cryptogenic hepatitis
2. By activity of process (defined by the index of histological activity – Knodell index):
 - periportal necroses of hepatocytes, including bridging necroses – 0-10 points
 - intralobular focal necroses and dystrophy of

- hepatocytes – 0-4 points
- inflammatory infiltrate in portal tracts -0-4 points
- fibroses – 0-4 points

1. By stage (METAVIR scale):

- 0 – fibrosis is absent
- 1 – mild periportal fibrosis
- 2 – moderate fibrosis with portal septa
- 3 – severe fibrosis with central septa
- 4 – cirrhosis

INTERNATIONAL CLASSIFICATION OF DISEASES 10 TH REVISION

Diseases of liver (K70-K77)

Excluded: hemochromatosis (E83.1)

jaundice (R 17)

Reye's syndrome (G93.7)

viral hepatitis (B15-B19).

Wilson's disease (E83.0)

K70 Alcoholic liver disease

K70.0 Alcoholic fatty liver

K70.1 Alcoholic hepatitis

K70.2 Alcoholic fibrosis and sclerosis of liver

K70.3 Alcoholic cirrhosis

K70.4 Alcoholic liver failure

K70.9 Alcoholic liver disease, unspecified

K71 Toxic liver damage

Included: caused by drugs:

- idiosyncratic (unpredictable) liver disease

- toxic (predictable) liver disease

Excluded: Alcoholic liver disease (K70. -)

- Budd-Chiari syndrome (I82.0)

K71.0 Toxic liver disease with cholestasis

K71.1 Toxic liver disease with hepatic necrosis

K71.2 Toxic liver disease with acute hepatitis

K71.3 Toxic liver disease with chronic persistent hepatitis

K71.4 Toxic liver disease with chronic lobular hepatitis

K71.5 Toxic liver disease with chronic active hepatitis

K71.6 Toxic liver disease with hepatitis, not classifiable under other headings

K71.7 Toxic liver disease with fibrosis and cirrhosis

K71.8 Toxic liver disease with other liver disorders

K71.9 Toxic liver damage, unspecified

K73 Chronic hepatitis, not elsewhere classified sections

Excluded: hepatitis (chronic):

alcohol (K70.1)

due medicinal preparations (K71.)

granulomatous NKIR (K75.3)

reactive nonspecific (K75.2)

virus (B15-B19)

K73.0 Chronic persistent hepatitis, not covered in other sections

K73.1 Chronic lobular hepatitis, not covered in other sections

K73.2 Chronic active hepatitis, not covered in other sections

K73.8 Other chronic hepatitis, not covered in other sections

K73.9 Chronic hepatitis, unspecified

K74 Fibrosis and cirrhosis

Excluded: alcoholic liver fibrosis (K70.2)

cardial liver sclerosis (K76.1)

cirrhosis (liver):

- Alcoholic (K70.3)

- congenital (R78.8)

with toxic lesion of liver (K71.7)

K74.0 Liver fibrosis

K74.1 Liver sclerosis

K74.2 Liver fibrosis with multiple sclerosis

K74.3 Primary biliary cirrhosis

K74.4 Secondary biliary cirrhosis

K74.5 Biliary cirrhosis, unspecified

K74.6 Other and unspecified cirrhosis

Etiology and pathogenesis of CH:

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) co-infection, and about 75% of cases of HCV infection become chronic. Hepatitis A and E viruses are not causes. Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.

Many cases are idiopathic. A high proportion of idiopathic cases have prominent features of immune-mediated hepatocellular injury (autoimmune hepatitis), including the following:

- The presence of serologic immune markers
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T lymphocytes and plasma cells in liver histologic lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, RA, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis). These conditions are called overlap syndromes.

Many drugs, including isoniazid, methyldopa, nitrofurantoin, and, rarely, acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Other causes of chronic hepatitis include alcoholic hepatitis and nonalcoholic steatohepatitis. Less often, chronic hepatitis results from α_1 -antitrypsin deficiency or Wilson's disease.

Cases were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. A more useful recent classification system specifies the etiology, the intensity of histologic inflammation and necrosis (grade), and the degree of histologic fibrosis (stage). Inflammation and necrosis are potentially reversible; fibrosis generally is not.

Treatment

- Supportive care
- Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for HBV, interferons for HCV)

Treatment goals include management of complications (eg, ascites, encephalopathy) and treatment of the cause. Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson's disease, should be treated. In chronic hepatitis due to HBV, prophylaxis for contacts of patients may be helpful; corticosteroids and immunosuppressive drugs should be avoided because they enhance viral replication. No prophylactic measures are required for contacts of patients with HCV infection.

Autoimmune hepatitis: Treatment should be based on severity of symptoms, degree of elevation in transaminases and IgG, histologic findings, potential side effects of treatment. Corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 40 mg per os once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. Some experts give concomitant azathioprine 1 to 1.5 mg/kg per os once/day; others add azathioprine only if low-dose prednisone fails to maintain suppression. Most patients require long-term, low-dose maintenance treatment. Liver transplantation may be required for end-stage disease.

HBV: Antiviral treatment is indicated for patients with elevated aminotransferase levels, clinical or biopsy evidence of progressive disease, or both. The goal is to eliminate HBV-DNA. Treatment may need to be continued indefinitely and thus may be very expensive; stopping treatment prematurely can lead to relapse, which may be severe. However, treatment may be stopped if HBeAg converts to anti-HBe or if tests for HBsAg become negative. Drug resistance is also a concern. Six antiviral drugs: entecavir, adefovir, lamivudine, interferon- α (INF- α), pegylated INF- α 2a (peginterferon- α 2a), and telbivudine - are available.

Comparison of Drugs Commonly Used to Treat Chronic Viral Hepatitis B*

Effect (% of patients)	Adefovir	Entecavir	Lamivudine	Pegylated Interferon- α 2a
Serum HBV-DNA becomes undetectable	21%	67%	44%	60%
HBsAg becomes undetectable	†	2%	†	3%
HBeAg becomes undetectable	24%	22%	32%	30%
ALT normalizes	48%	68%	41%	39%
Histologic improvement occurs	53%	72%	49–56%	38%
Resistance develops	At 1 yr: 0% At 5 yr: 15%	At 2 yr: 0%	At 1 yr: 14% At 5 yr: 69%	None

*Telbivudine is a new drug for which sufficient data are not yet available.

*Data are insufficient.

HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

First-line treatment is usually with an oral antiviral drug, such as entecavir (a nucleoside analogue) or adefovir (a nucleotide analogue). Combination therapy has not proved superior to monotherapy.

Entecavir appears to have higher antiviral potency than other commonly used drugs. Resistance to entecavir is uncommon, but the drug has not been in widespread clinical use for very long. Dosage is 0.5 mg per os once/day; however, patients who have previously taken a nucleoside analogue should take 1 mg per os once/day. Dose reduction is required in patients with renal insufficiency. Serious adverse effects appear to be uncommon so far, although the drug can induce tumors in animals.

Adefovir is also relatively potent. Dosage is 10 mg per os once/day. Adefovir may cause renal dysfunction, so serum creatinine level must be measured periodically and the dose reduced if necessary. Tenofovir appears to be replacing adefovir. Tenofovir has superior

efficacy (eg, as measured by rates of undetectable HBV-DNA and HBsAg) and comparable safety. The dose is 300 mg once/day. Alternatively, lamivudine (a nucleoside analogue) 100 mg per os once/day is given. It has few adverse effects, which is one of its advantages over other antiviral drugs used to treat chronic HBV infection. INF- α (usually IFN- α 2b), formerly first-line treatment, can be used. Dosage is 5 million IU subcutaneously once/day or 10 million IU subcutaneously 3 times/week for 4 months. In about 40% of patients, this regimen eliminates HBV-DNA and causes seroconversion to anti-HBe; a successful response is usually presaged by a temporary increase in aminotransferase levels. The drug must be given by injection and is often poorly tolerated. The first 1 or 2 doses cause an influenza-like syndrome. Later, fatigue, malaise, depression, bone marrow suppression, and, rarely, bacterial infections or autoimmune disorders can occur. In patients with advanced cirrhosis, IFN- α can precipitate hepatic failure and is therefore contraindicated. Other contraindications include renal failure, immunosuppression, solid organ transplantation, cytopenia, and substance abuse. In a few patients, treatment must be stopped because of intolerable adverse effects. The drug should be given cautiously or not at all to patients with ongoing substance abuse or a major psychiatric disorder.

Pegylated IFN- α 2 can also be given. Dosage is 180 μ g sc once/wk. Adverse effects are similar to those of IFN- α but may be less severe.

Telbivudine is a new drug that has greater efficacy than lamivudine but has high rates of resistance.

Liver transplantation should be considered for end-stage liver disease caused by HBV, but the infection aggressively attacks the graft, and prognosis is less favorable than when liver transplantation is done for other indications. Long-term posttransplantation therapy with lamivudine improves the outcome.

HCV: For chronic hepatitis due to HCV, treatment is indicated if aminotransferase levels are elevated and biopsy shows active inflammatory disease with evolving fibrosis. Treatment aims to permanently eliminate HCV-RNA (sustained response), which is associated with permanent normalization of aminotransferase and cessation of histologic progression.

Combination therapy with pegylated IFN- α plus ribavirin is given. Pegylated IFN- α 2b 1.5 μ g/kg sc once/week and pegylated IFN- α 2a 180 μ g subcutaneously once/week have comparable results. Ribavirin 500 to 600 mg po bid is usually given, although 400 mg 2/day may be sufficient for viral genotypes 2 and 3.

HCV genotype and viral load are determined before treatment because results influence treatment. Genotype 1 is the most common type but is more resistant to treatment with pegylated IFN- α plus ribavirin (dual therapy) than other genotypes. A protease inhibitor is added (triple therapy); it increases the rate of sustained response from < 50% (with dual therapy) to 70 to 80%. If telaprevir is chosen, it is given at a dose of 750 mg per os 3/day for 12 weeks. The HCV-RNA level should be measured 4 and 12 weeks after beginning treatment. If HCV-RNA is undetectable at 4 and 12 weeks, triple therapy is followed by

another 12 weeks of dual therapy with pegylated interferon and ribavirin (total treatment duration of 24 weeks). However, dual therapy should be continued for 36 weeks after triple therapy (total treatment duration of 48 weeks) if patients have the following:

- No response to previous antiviral therapies (HCV-RNA did not decrease by at least 2 log levels after treatment for 12 weeks) or an incomplete response (called partial responders)
- HCV-RNA that is detectable at 4 or 12 weeks after beginning triple therapy
- Compensated cirrhosis

If boceprevir is chosen, it is always given at 800 mg per os 2/day, beginning 4 weeks after starting dual therapy with pegylated IFN- α plus ribavirin. The HCV-RNA level should be measured 4, 8, 12, and 24 weeks after beginning treatment. If HCV-RNA is undetectable at 8 and 24 week, triple therapy is given for 24 weeks (total treatment duration of 28 weeks). In certain cases, treatment duration is increased, as follows:

- If patients responded only partially to previous antiviral therapy and have no detectable HCV-RNA at 8 or 24 week: 32 weeks of triple therapy (total treatment duration of 36 weeks)
- If patients have detectable HCV-RNA at 8 week: 32 weeks of triple therapy, followed by 12 weeks of dual therapy (treatment duration of 48 weeks)
- If patients have detectable HCV-RNA at 4 week and are tolerating triple therapy: 44 weeks of triple therapy (total treatment duration of 48 weeks)
- If patients have not responded to previous antiviral therapy or have compensated cirrhosis: 44 weeks of triple therapy (total treatment duration of 48 weeks)

Combination therapy with pegylated IFN- α plus ribavirin is given for 1 year for genotypes 2, 3, or 4; a sustained response rate of about 45 to 50% overall occurs. Results are more favorable in patients with early disease and less favorable in those who already have cirrhosis. HCV viral load should be measured at 3 month and treatment stopped if RNA has not declined by at least 2 log levels compared with pretreatment values.

Less common genotypes 2 and 3 respond more favorably to treatment with pegylated IFN- α plus ribavirin. Combination therapy is required for only 6 months and gives an overall sustained response rate of about 75%. Longer treatment does not improve the results.

Adverse effects of pegylated IFN are similar to those of IFN- α but may be less severe; contraindications are also similar (see above).

Ribavirin is usually well tolerated but commonly causes anemia due to hemolysis; dosage should be decreased if hemoglobin falls to < 10 g/dL. Ribavirin is teratogenic for both men and women, necessitating contraception until 6 months after completion of treatment. Patients who cannot tolerate ribavirin should be given pegylated IFN- α , but results are not as good as with combination treatment. Ribavirin monotherapy is of no value.

Telaprevir and boceprevir can cause anemia. Telaprevir can also cause rashes, including Stevens Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis; deaths have occurred. Both drugs can result in numerous drug-drug interactions.

In most adult transplantation centers, advanced cirrhosis due to HCV is now the most common indication for liver transplantation. Although HCV recurs in the graft, the course is usually indolent, and long-term survival rates are relatively high.

Prognosis

Prognosis is highly variable. Chronic hepatitis caused by a drug often regresses completely when the offending drug is withdrawn. Without treatment, cases caused by HBV can resolve (uncommon), progress rapidly, or progress slowly to cirrhosis over decades. Resolution often begins with a transient increase in disease severity and results in seroconversion from hepatitis B e antigen (HBeAg) to antibody to hepatitis B e antigen (anti-HBe). Co-infection with HDV causes the most severe form of chronic HBV infection; without treatment, cirrhosis develops in up to 70% of patients. Untreated chronic hepatitis due to HCV produces cirrhosis in 20 to 30% of patients, although development may take decades. Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular cancer. The risk is also increased in chronic HCV infection, but only if cirrhosis has already developed.

Control of the initial level of knowledge on the topic "Chronic hepatitis":

1. The indicator enzymes include:
 - A. Choline esterase, ceruloplasmin
 - B. Alkaline phosphatase, 5-nucleotidase
 - C. ALT, AST, aldolase, glutamatdehydrogenase
 - D. Creatine phosphokinase, lipase
 - E. Amylase, elastase

2. Excretory enzymes include:
 - A. Choline esterase, ceruloplasmin
 - B. Alkaline phosphatase, 5-nucleotidase, gamma glutamattranspeptidase
 - C. ALT, AST, aldolase, glutamatdehydrogenase
 - D. creatine phosphokinase, lipase
 - E. amylase, elastase

3. Incretory enzymes include:
 - A. Alkaline phosphatase, 5-nucleotidase, gamma glutamattranspeptidase
 - B. Choline esterase, ceruloplasmin
 - C. ALT, AST, aldolase, glutamatdehydrogenase
 - D. creatine phosphokinase, lipase
 - E. amylase, elastase

4. What biochemical syndromes are typical for chronic hepatitis?
 - A. Syndrome of cytolysis and hepatic hiperazotemia
 - B. Syndrome of synthetic liver function deficiency and cytolysis
 - C. Cholestasis syndrome and immune inflammation
 - D. All of the mentioned above
 - E. None of the mentioned above

5. What clinical syndrome is most typical for chronic hepatitis?
 - A. Pain
 - B. Articular
 - C. Fever
 - D. Asthenovegetative
 - E. Encephalopathic

6. Etiologic factors of chronic hepatitis are:
 - A. Viruses, bacteria, giardia
 - B. Smoking, obesity, viruses
 - C. Viruses, hepatotropic drugs, alcohol
 - D. Hepatoprotectors, viruses, bacteria
 - E. Radiation, obesity, protozoa

7. What is typical for the syndrome of "small liver failure?"
- A. Insomnia, itchy skin, swelling
 - B. Drowsiness, enlargement of the liver, leukocytosis
 - C. Drowsiness, transient jaundice, increased bleeding
 - D. Insomnia, ascites, "liver signs"
 - E. ascites, portal hypertension, spider angiomas
8. What changes in the liver does virus replication induce in patients with chronic hepatitis B?
- A. Direct cytotoxic action
 - B. Lesion of intrahepatic ducts
 - C. Immune disorders and the development of vasculitis
 - D. Lesion of nervous system of the liver
 - E. Stasis of bile
9. What are the diagnostic criteria for autoimmune hepatitis diagnosis?
- A. Cholestasis, the efficacy of the choleretics
 - B. hypergammaglobulinemia, accelerated ESR, the efficacy of glucocorticoids
 - C. Enlarged liver, elevated transaminases and alkaline phosphatase in the blood
 - D. Enlarged liver, increased bilirubin, efficacy of hepatoprotectors
 - E. Efficacy of antiviral drugs, vitamins
10. What biochemical changes are typical for cytolysis syndrome?
- A. Increased alkaline phosphatase, decreased total protein and cholesterol
 - B. Reduction of iron and prothrombin, increased cholesterol
 - C. Increased AST, ALT, LDG
 - D. Increased alkaline phosphatase, prothrombin, bilirubin
 - E. Reduction of prothrombin and transaminases, increased bilirubin

Control of the final level of knowledge on the topic "Chronic hepatitis"

1. What drugs are the most likely causative agents for drug-induced chronic hepatitis?
 - A. Antibiotics of penicillin group
 - B. Non-steroidal anti-inflammatory drugs
 - C. Tuberculostatic drugs, contraceptives
 - D. Cardiac glycosides
 - E. Calcium antagonists, beta-blockers

2. What causes pain in chronic hepatitis?
 - A. stagnation of bile in the bile ducts
 - B. stretching of liver capsule
 - C. concomitant cholecystitis
 - D. concomitant pancreatitis
 - E. Portal hypertension

3. What is the reason for dyspeptic syndrome in chronic hepatitis?
 - A. Lesion of bile ducts
 - B. Impaired disintoxication liver function
 - C. Cholestasis
 - D. concomitant chronic pancreatitis
 - E. disbacteriosis

4. What extrahepatic lesions are most frequently observed in chronic hepatitis?
 - A. Cardiac
 - B. iridocyclitis
 - C. polyarthritis, myositis
 - D. Dermatitis
 - E. Nephrotic Syndrome

5. What etiology of chronic hepatitis favors development of extrahepatic lesions the most?
 - A. Chronic viral hepatitis B
 - B. Chronic hepatitis C
 - C. Drug-induced chronic hepatitis
 - D. Autoimmune chronic hepatitis
 - E. Cryptogenic chronic hepatitis

6. Which groups of drugs are used in the treatment of autoimmune chronic hepatitis?
 - A. Hepatoprotectors, choleretics
 - B. Spasmolytics, cholekinetics
 - C. Glucocorticoids, immunosuppressants
 - D. Antiviral drugs, H₂-histamine receptors blockers
 - E. Coating drugs, vitamins

7. What type of diet should be prescribed to patients with chronic hepatitis?
- A. 3rd
 - B. 4th
 - C. 5th
 - D. 2nd
 - E. 1st
8. What instrumental studies are needed to confirm the diagnosis of "chronic hepatitis"?
- A. Radiography of the digestive system
 - B. Laparoscopy
 - C. Ultrasonography of the abdomen
 - D. Duodenal probing
 - E. pH-metry
9. What is the mechanism for development of edematous-ascitic syndrome in patients with chronic hepatitis?
- A. kidney function insufficiency
 - B. Reduced plasma oncotic pressure
 - C. circulation failure
 - D. liver function failure
 - E. adrenal glands failure
10. Which group of drugs should be prescribed for the treatment of viral hepatitis?
- A. Antibiotics, hepatoprotectors
 - B. choleretics, hepatoprotectors
 - C. Interferons, hepatoprotectors
 - D. Vitamins, enzymes
 - E. Detoxification and immunomodulators

Case-based questions

1. Patient, 44 years old, complains on intense pain in the upper abdomen radiating to the left upper quadrant, loss of appetite, belching. As a child was sick with viral hepatitis type B. 4 years ago she was operated due to cholelithiasis. Objective data: yellow sclera, pain during palpation around the navel and at the point of Mayo-Robson. CBC: $L - 9.7 \times 10^9 / L$, the differential is not changed, ESR - 18mm/hr. Urine diastase- 320 units. What disease should be considered first for differential diagnosis?

- A. Chronic pancreatitis.
- B. Chronic cholangitis
- C. Chronic gastritis
- D. Chronic colitis
- E. Chronic hepatitis

2. Man '40 suffers from autoimmune hepatitis. Biochemical assay: A / G ratio 0.8, total bilirubin - 42 mmol / L, ALT - 23 mmol / L, AST - 1.8 mmol / l. Which of the following would be the most effective treatment:

- A. Antibacterial agents
- B. Glucocorticoids, cytostatics
- C. Hepatoprotectors
- D. Antiviral drugs
- E. Vitamin E.

3. Woman, 37, visited doctor due to the exacerbation of chronic hepatitis. The blood assay showed increased level of indirect bilirubin, AST, ALT; decrease of albumin, and prothrombin. What pathological process is the most likely reason for these changes?

- A. Cytolysis
- B. Cholestasis
- C. Portal hypertension
- D. Hypersplenism
- E. Derangement of hemostasis

4. The patient, 32 years old, with chronic viral hepatitis complains on a dull aching pain in the right upper quadrant, nausea, dryness in mouth. Liver size according to Kurlov: 13 - 12 - 11 cm, spleen enlarged 2cm above normal, AST - 3.2 mmol / h * l, ALT - 4.8 mmol / h * l. Serological assay: HBeAg, high concentration of DNA - HBV. Which of the following drugs is the drug of choice for the treatment of this patient?

- A. arabinoside monophosphate
- B. Acyclovir
- C. Remantadin
- D. α -interferon
- E. essentielle forte

5. Student, 20, was on outpatient treatment for 3 days due to respiratory infection and an increase of body temperature up to 38° C. He complains on a poor appetite, tiredness at normal body temperature and missing catarrhal symptoms of upper respiratory tract infections. The doctor found an increase of liver size and a moderate liver tenderness. The new cases of hepatitis A were revealed at university recently. Which method would identify the cause of this condition most precisely?

- A. Immunofluorescent study of nasopharyngeal swabs
- B. Determination of bilirubin in the blood
- C. Determination of the β -lipoprotein
- D. Liver ultrasound
- E. Determination of aminotransferase level in blood.

6. Patient, 44 years old, had long term alcohol abuse. Objective data: thenar and hypothenar are of pink color, spider angiomas on the anterior surface of the chest, enlarged veins on anterior abdominal wall. Abdomen is swollen; there is free fluid in the abdominal cavity. Liver is 4 cm enlarged above normal size, compacted, smooth, painless. Spleen edge is palpable. CBC: L - $8.7 \times 10^9 / l$. What complication has developed in this patient?

- A. coagulopathy
- B. Subacute hepatic dystrophy
- C. Portal hypertension
- D. Thrombosis of mesenteric vessels
- E. hypersplenism

7. Patient, 35 years old, was brought to the hospital in severe condition. It is 6th day of disease. The disease began acutely with fever up to 38.0 C, joint pain, general weakness, loss of appetite, vomiting. On day 2, urine became dark, on the third day - the sclera jaundice appeared, later the skin became yellow as well. Objective data: weakness, disorientation, sleep inversion, intense jaundice of sclera, skin hemorrhages, reduction of liver size, nausea and anorexia. Prothrombin index - 45%. In history: 4 months ago was operated due to perforated ulcer. During surgery a blood transfusion was performed. What causes this condition?

- A. Acute vascular insufficiency
- B. Perforation of intestine
- C. Infectious and toxic shock
- D. Acute hepatic encephalopathy
- E. Side effects of medications.

8. Patient, 40 years old, complains of pruritus, jaundice, heaviness in the right upper quadrant and weakness. Skin is yellow, signs of excoriations, liver + 5 cm; the size of the spleen is 6x8 cm. Liver test: alkaline phosphatase - 4.0 mmol / L, total bilirubin – 60 mmol / l, cholesterol - 8 mmol / l. What is the leading syndrome in a patient:

- A. hepatolienal
- B. cytolytic
- C. mesenchymal-inflammatory
- D. cholestatic

E. Hepatocellular failure

9. Patient C, 24 years old, complains on pain in the right upper quadrant and joints, skin jaundice, weight loss of 10 kg during last year, increase of body temperature up to 38°C. She became sick after delivery six months ago. Objective data: yellow skin and sclera, xanthoma on the eyelids, liver +4 cm, spleen + 2 cm and tender. Biochemical assay: ALT - 3.4 mmol / L, AST - 2.8 mmol / l, total bilirubin - 96 mmol / l, unconjugated bilirubin - 54 mmol / l; HBs Ag was not found. What is the main pathogenetic mechanism of the disease?

- A. Fatty liver
- B. Toxic liver damage
- C. Autoimmune
- D. Cholestasis
- E. Viral infection

10. Patient, 36 years old, complains on general weakness, irritability, heaviness in the right upper quadrant, subfebrile body temperature. He had viral hepatitis 4 years ago. These complaints have been gradually developing during the last 3 months. Objective data: Liver + 3 cm. Laboratory data: total bilirubin 64.5 mmol / l; direct - 22.7 mmol / l; γ -globulins - 31%, AST - 1.42 mmol / h * l, ALT - 1.96 mmol / h * l. Signs of active viral replication (HBeAg - positive reaction). What drug would be the most effective for treatment of this patient?

- A. Essentiale forte
- B. Karsil
- C. Levamisole
- D. Prednisolone
- E. α -interferon.

CORRECT ANSWERS «Chronic hepatitis»

Initial level of knowledge

1. C	6. C
2. B	7. C
3. B	8. C
4. D	9. B
5. D	10. C

Final level of knowledge

1. C	6. C
2. B	7. C
3. B	8. C
4. C	9. B
5. D	10. C

Case-based questions

1. A	6. D
2. B	7. D
3. A	8. D
4. D	9. C
5. E	10. E

Control questions:

1. Definition of CH
2. The main clinical syndromes of CH
3. Description of biochemical syndromes in CH
4. Description of physical data in CH
5. The peculiarities of viral hepatitis
6. The peculiarities of toxic hepatitis
7. The peculiarities of autoimmune hepatitis
8. Diagnostic methods in CH
9. Complications of CH.
10. Principles of treatment of viral CH
11. Principles of treatment of autoimmune CH
12. Lifestyle and diet therapy in CH.
13. Pharmacological treatment in CH
14. Prevention of CH

Practical tasks.

1. Supervise patient with CH
2. Interpret the laboratory data.
3. Interpret the data of instrumental methods.
4. Perform differential diagnosis of CH
5. List complications of CH
6. Write recipes for pharmacological therapy of CH.

Further reading:

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