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МЕТОДИЧНІ РЕКОМЕНДАЦІЇ
ДЛЯ СТУДЕНТІВ з англомовною формою навчання

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Змістовний модуль №2	Основи діагностики, лікування та профілактики основних хвороб органів травлення
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KHARKOV NATIONAL MEDICAL UNIVERSITY

DEPARTMENT OF INTERNAL MEDICINE N3

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

Liver cirrhoses

Kharkiv 2014

Module "Fundamentals of diagnosis, treatment and prevention of major diseases of digestive tract".

Topic "Liver cirrhoses" (LC).

Topicality

Despite of considerable success in diagnosis of diseases of digestive tract sometimes it is impossible to make a certain diagnosis on practice. This basically applies to the chronic diffuse diseases of liver (CDDL)-(LC) that occur with relatively nonspecific clinical symptoms (discomfort in the right upper quadrant, fatigue, jaundice, hepatomegaly, biochemical changes, etc.). Often a doctor, not being able to perform morphological study of the liver, i.e. the fine needle biopsy (FNB), formulates diagnosis empirically, and thus diagnosis has insufficient evidentiary level.

About 2 million people die annually all over the world from cirrhosis and viral hepatocarcinoma. Mortality associated with alcoholic LC in developed countries is similar to that of viral LC.

Aims of teaching:

- To teach students to recognize basic symptoms and syndromes of LC.
- To acquaint students with physical methods of study in CL.
- To acquaint students with methods of study which are used for the diagnosis of LC, indications and contra-indications for their conducting, techniques of their performance, diagnostic value of each of them.
- To teach students to interpret the results of the conducted studies independently.
- To teach students to recognize and diagnose complications of LC.
- To teach students to prescribe treatment for LC.

What should a student know?

- Incidence of LC.
- Etiologic factors of LC.
- Pathogenesis of LC.
- Basic clinical syndromes of LC.
- General and alarm symptoms of CL.
- Physical symptoms of LC.
- Diagnosis of LC.
- Morphological studies of liver (biopsy) in LC.
- Instrumental methods of LC diagnosis.
- Differential diagnosis of LC.
- Classification of LC.
- Complications of LC.
- Treatment of LC (change of lifestyle, a balanced diet, medicinal therapy).

What should a student be able to do?

- To distinguish basic clinical and physical syndromes of LC.
- To interpret the results of biochemical and immunoenzyme assays.
- To interpret the data of liver biopsy.

- To interpret the results of instrumental methods of study of liver.
- To estimate the accordance of a certain patient to the criteria of successful therapy.
- To perform the differential diagnosis.
- To prescribe the treatment to patients with LC.

The list of practical skills, which a student should possess:

- Inspection of abdomen.
- Examination of abdomen.
- Superficial palpation of stomach.
- Deep methodical sliding palpation of abdomen according to Obraztsov- Strazhesko method.
- Examination of skin and mucosa.
- Physical data of liver inspection.

Contents of topic on LC:

Cirrhosis is a progressive diffuse polyetiological chronic liver disease, which is characterized by a significant decrease in the mass of functioning hepatocytes, expressed fibrosis with impaired hepatic lobes structure and damaged vasculature of liver.

Etiology and pathogenesis of LC.

LC is the final stage in the evolution of many inflammatory-necrotic and necrotic degenerative pathological processes in the liver. Posthepatitis LC composes 50-80% of all cases. Viral LC is the result of viral hepatitis, tuberculosis also may have some importance, as well as lues, brucellosis, parasite invasion, especially opisthorchiasis. Nutritional problems may also contribute to cirrhotic transformation - protein deficiency, deficiency of vitamins (especially B_{12}, B_6, E), alcohol abuse. Separate group of patients with LC are the ones who suffer from systemic diseases of connective tissue - lupus, rheumatoid arthritis. In 40% of patients with LC etiology remains unclear.

The leading role in the mechanism of alcohol LC belongs to repeated attacks of acute alcoholic hepatitis. Progression of disease is associated with necrosis of liver parenchyma, increased collagen synthesis, reduction and distortion of liver regeneration. Necrosis of hepatocytes is caused by the influence of ethanol and its metabolic products. As the result, an acute increase in the synthesis of collagen caused by tissue hypoxia occurs, as well as stimulation of collagen production by decay products of hepatocytes. A powerful stimulant of fibrous tissue is alcoholic hyalin. In addition, alcohol blocks the degradation of collagen. An important factor that promotes transformation of alcoholic liver fibrosis into cirrhosis is perivenular sclerosis. Development of expressed fibrosis around central veins causes early postsinusoidal portal hypertension. Ethanol also inhibits the regeneration of damaged liver due to the injury of hepatocytes' mitochondria, impaired metabolism of proteins and nucleic acids.

Some importance belongs to pathological immune reactions - production of antibodies against liver cells, the immune complexes, antibody-dependent cytolysis of hepatocytes. Necrosis of hepatocytes under the influence of alcohol is the result of a direct toxic damage and immune cytolysis. Alcohol hyalin is an antigen that activates the reaction of humoral and cellular immunity. The content of antigen of alcohol hyalin (AgAH) and antibodies to it (AbAH) has a tendency to increase in the serum of patients with alcoholic hepatitis. Along the progression of the disease the titer of AgAH decreases and titer of AbAH increases dramatically. The immune complexes AgAH + AbAH, which belong to immunoglobulins A and G can be found in the liver of patients with acute alcoholic hepatitis or active alcoholic LC. These immune complexes cause chemotaxis of cells which possess cytotoxic activity and provoke necrosis of hepatocytes. T-lymphocytes (90%) dominate in the infiltrates of portal stroma of liver in alcoholic hepatitis, most of them are cytotoxic against autologous liver cells. Lymphokines secreted by sensitized lymphocytes are the additional factors of fibrogenesis. Lymphocytes of infiltrates, which are sensitized to alcohol hyalin show cytotoxicity towards cells that contain alcohol hyalin.

The mechanism of alcoholic LC development without attacks of acute alcoholic hepatitis is also possible. It is caused by progressive pericellular and perivenular fibrosis, which leads to the formation of fibrous septa that divide the parenchyma. Disruption of normal flow of blood, lymph, bile leads to severe necrotic lesions with secondary inflammatory infiltration and development of LC.

The pace of LC development depends primarily on the level of activity of preceding hepatitis. LC in patients with chronic active hepatitis of moderate activity develops more slowly than at high activity. Transformation pace decreases during treatment with immunosuppressants. The immune component of pathologic process has higher significance at early stages of LC. A persistent virus dwells in hepatocytes, which induces the immune liver damage - the immune cytolysis of hepatocytes. Stepwise necroses of liver lobules with their secondary inflammatory infiltration develop. In viral cirrhosis infiltrates consist mostly of lymphocytes, macrophages, and plasma cells.

At later stages of the disease an ischemic liver damage comes to the forefront, which often is not only crucial, but also the only factor for progression of cirrhosis. Ischemic liver damage is caused by vascular reconstruction of organ due to poor circulation in the sinusoids of liver lobules. Sinusoids and perisinusoidal spaces are filled with collagen fibers, which complicate blood flow. Sinusoidal and perisinusoidal portal hypertension develops. Fibrosis, "capillarization" of sinusoids causes hypoxic damage of hepatocytes and their necrosis followed by their replacement to connective tissue. Hypoxia increases severity of fibrogenetic processes. Sclerosis of liver sinusoids is a morphological marker of cirrhotic transformation of the liver. After the occurrence of sinusoidal portal hypertension the vascular anastomoses begin to form around lobules, which provide bypass blood flow from branches of the hepatic artery and portal vein into hepatic venous system, thus bypassing the liver lobules. Blood circulation in portal vein branches is largely blocked by cell infiltrates, fibrous tissue, and false lobules. Therefore, portal vein venous blood is shunted by intrahepatic porto-central and extrahepatic porto-caval anastomoses. Blood supply of impaired lobules is mainly provided by arterial blood – lobules are surrounded by a powerful vascular anastomoses system, which are mainly arterial. Exclusion of significant part of liver parenchyma from blood supply due to shunting of blood is accompanied by an acute progression of liver failure.

Impaired architectonics of liver lobules is accompanied by deformation, obstruction of bile ducts lumen. False lobules and fibrous septa cause obstruction of larger bile ducts – as the result peripheral cholestasis develops, which deepens the injury of hepatocytes.

CLASSIFICATION OF LC:

- **By etiology:**
  - viral hepatitis B, C, D
  - alcohol-induced liver injury
  - drug- or toxin-induced liver injury
  - autoimmune hepatitis
  - metabolic diseases (α1AT deficiency, hemochromatosis, Wilson's disease)
  - nonalcoholic steatohepatitis or fatty liver
  - biliary disorders (primary and secondary biliary cirrhosis, primary sclerosing cholangitis)
  - vascular derangements (chronic right-sided heart failure, Budd-Chiari syndrome)

- **By morphology:**
  - micronodular (diameter of nodules up to 3 mm)
  - macronodular (diameter of nodules over 3 mm)
  - mixed

- **By clinical signs:**

1. Stage of disease according to Child-Pugh criteria:

Parameter	**Numerical score**		
	1	2	3
Bilirubin, mcmol/l	< 34,2	34,2-51,3	>51,3
Albumin, g/l	>35	28-35	<28
Prothrombin index, %	80-60	60-40	<40
Ascites	none	slight	moderate/severe
Encephalopathy	none	minimal	severe (coma)
Total numerical score		**Child-Pugh class**	
5-6		A	
7-9		B	
10-15		C	

2. Activity of process:
- active
- non-active

3. Complications:
- portal hypertension
- bleeding from esophageal/stomach varices
- hepatic encephalopathy
- spontaneous bacterial peritonitis
- hepatorenal syndrome
- hepatocellular carcinoma
- thrombosis of portal vein

CLINICAL SYMPTOMS OF LC:

- Early: GI disturbances, dull pain in RUQ/epigastrium, fever, malaise, enlargement of liver & spleen
- Late: Jaundice, skin lesions (spider angiomas, palmar erythema), skin itch, coagulopathy, endocrine disturbances, peripheral neuropathy, ascites, prominent abdominal veins.

Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss. The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.

Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren's contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.

Once complications of cirrhosis develop, decompensation inexorably ensues.

CLINICAL SYNDROMES OF LC:

SYNDROMES	%
Asthenic	90
Hepatolienal	80-90
Pain syndrome in RUQ	80
Dyspeptic (nausea, vomiting, bloating, decrease of appetite, weight loss)	60-80
Jaundice	60-70
Edematic syndrome, ascites	50-60
Hemorrhagic (bleeding sickness)	30-40
Minor liver stigmata	30-40
Subfebrile fever	30-50
Endocrine disorders (gynecomastia, testicular atrophy, hyperaldosteronism)	30-40
Skin itch	30
Hepatic encephalopathy	20-30

Complications: *Portal hypertension* is the most common serious complication; it can manifest as GI bleeding from esophageal, gastric, or rectal varices or portal hypertensive gastropathy. Bleeding rarely occurs unless the portal pressure gradient is >12 mm Hg (normal portal pressure is 5 to 10 mm Hg). Portal hypertension can be massive.

Cirrhosis can cause other cardiovascular complications. Vasodilation and intrapulmonary right-to-left shunting and ventilation/perfusion mismatch can result in hypoxia (*hepatopulmonary syndrome*). A cardiac myopathy can also accompany cirrhosis.

Ascites can develop, with a risk of spontaneous bacterial peritonitis. Splenic congestion with hypersplenism may occur, resulting in splenomegaly, platelet sequestration, and consequent cytopenia.

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, renal failure (hepatorenal syndrome), and hepatic encephalopathy.

Hepatorenal syndrome: This syndrome consists of progressive oliguria and azotemia in the absence of structural damage to the kidney; it usually occurs in patients with fulminant hepatitis or advanced

cirrhosis with ascites. Its unknown pathogenesis probably involves extreme vasodilation of the splanchnic arterial circulation, leading to decreased central arterial volume. Neural or humoral reductions in renocortical blood flow follow, resulting in a diminished glomerular filtration rate. Low urinary Na concentration and benign sediment usually distinguish it from tubular necrosis, but prerenal azotemia may be more difficult to distinguish; in equivocal cases, response to a volume load should be assessed. Once established, renal failure due to untreated hepatorenal syndrome is usually rapidly progressive and fatal (type 1 hepatorenal syndrome), although some cases are less severe, with stable milder renal insufficiency (type 2).

Malabsorption; Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis. Clotting may be impaired because of coagulopathy or thrombocytopenia. Coagulopathy results from impaired hepatic synthesis of the factors necessary for clotting, malabsorption of vitamin K due to impaired bile secretion into the duodenum, or both. Thrombocytopenia may be caused by hypersplenism (platelet sequestration), alcohol excess (directly inhibiting the bone marrow), or both. Pancytopenia also occurs with alcoholism.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B and C viruses, hemochromatosis, alcohol-related liver disease, α_1-antitrypsin deficiency, or glycogen storage disease.

ADDITIONAL DIAGNOSTIC TESTS:

- Liver function tests, coagulation tests, CBC, and serologic tests for viral cause.
- Sometimes biopsy
- Identification of cause based on clinical evaluation and selective testing

Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (eg, hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis. Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis—usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing

factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may also detect leukopenia, thrombocytopenia, or pancytopenia.

Diagnostic imaging: Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites.

CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99 sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

Identification of the cause: Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing. Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis.

Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C.

If common causes such as alcohol or viral hepatitis are not confirmed, other less common causes are sought:

- Presence of antimitochondrial antibodies (in 95%) suggests primary biliary cirrhosis.
- Strictures and dilations of the intrahepatic and extrahepatic bile ducts seen on magnetic resonance cholangiopancreatography (MRCP) suggest primary sclerosing cholangitis.
- Increased serum Fe and transferrin and possibly results of genetic testing suggest hemochromatosis.
- Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson's disease.
- Hypergammaglobulinemia and presence of autoantibodies (eg, antinuclear or anti–smooth muscle antibodies) indicate autoimmune hepatitis.

Liver biopsy: If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. Its sensitivity approaches 100%. Nonalcoholic steatohepatitis (NASH), often associated with obesity, diabetes, or the metabolic syndrome, may be evident on ultrasound scans but requires liver biopsy for confirmation. In obvious cases of cirrhosis with a marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required when results would not change management .

Surveillance: Patients with cirrhosis, particularly if due to chronic viral hepatitis B or C or hemochromatosis, should be screened for hepatocellular carcinoma (eg, measuring α-fetoprotein levels and ultrasonography every 6 to 12 months

TREATMENT

- Diet (proteins 0,5g/kg), supplemental vitamins.
- Alcohol and hepatotoxic substances must be avoided, injurious drugs should be stopped
- Treatment of a cause – viral cirrhosis should be treated with the same etiological treatment as chronic viral hepatitis.

BASIC THERAPY:

HEPATOPROTECTORS:

- Herbal: silimarin (Silibor, Silimarin), artichoke extract (Chofitol) 1-2 tablets 3/day, course 1-2 months
- Preparations of essential phospholipids: Essentiale, Essentiale-forte H, Enerliv 1-2 vials i/v - 10 days, then 1-2 capsules 3/day, course 1-2 months
- Lipoic acid (Berlition, Espa-lipon) 600mg i/v 10 days, then 600mg (1 tablet) 1/day, course 1 month
- Ademetionin (Heptral) 800mg i/v or intramuscularly – 14 days then orally 800 mg 2/day, course 1-2 months

ENZYME PREPARATIONS: (Mesim-forte, Pangrol, Creon) 1-2 tablets 3/day during meals

PATHOGENETIC THERAPY:

GLUCOCORTICOIDS – indicated for patients with hepatocellular insufficiency, cholestasis, viral infection (especially hepatitis C), pre- or hepatic coma, high activity of transaminases > 2,5 times

- Prednisolone (Prednisolone) 30-60-90mg orally or i/v, course 3-4 weeks, then gradually decrease to 5 mg/day

- Methylprednisolone (Metipred) 4-8mg/day; course 3-4 weeks, then gradually decrease to 4 mg/day

DISINTOXICATION THERAPY - indicated for patients with hepatocellular insufficiency, cholestasis, pre- or hepatic coma.

- dextrose solution 5-10% 200-400ml + vitamin C i/v dropper
- Ringer solution 100-200ml i/v dropper, NaCl 0,9% 200-400ml + vitamin C i/v dropper
- albumin 10% 100-200ml i/v dropper
- solution of aminoacids (reosorbilakt) 200-400ml i/v dropper

MANAGEMENT OF COMPLICATIONS

CHOLESTASIS: Ursodeoxycholic acid (10-12 mg/kg during 1-2 months), preparations of calcium and fat-soluble vitamins A, E, D, K.

ASCITES/EDEMA:

- Sodium/fluid restriction
- Diuretics: spironolactone (veroshpiron) 50-100-200mg 2/day, max dose – 400mg/day
- If effect is absent: veroshpiron (100-200mg) + furosemide (20-160mg) or lasix 20-40mg i/v in the morning (under control of diuresis and electrolyte balance)
- Paracentesis (in case of refractory ascites)
- Bacterial ascites/peritonitis: cefalosporins (3^{rd} generation preferably – ceftazidin 1g 2/day intramuscularly) + syntetic penicillin – amoxicillin (Amoxiclav) 500mg 4/day or 1g 2/day i/v, course 7-10 days
- Peritoneovenous shunt – continuous reinfusion of ascitic fluid into the venous system

PORTAL HYPERTENSION – the aim of treatment is to decrease portal venous pressure.

β-adrenoblockers: Propranolol 40-80 mg per os 2/day, Nadolol 40-160 mg per os once/day, Carvedilol 6.25 to 12.5 mg per os 2/day with or without nitrates (Isosorbid mononitrate) 10 to 20 mg per os 2/day.

Patients who do not adequately respond to either treatment should be considered for transjugular intrahepatic portosystemic shunting (TIPS) or, less frequently, a surgical portacaval shunt. In TIPS, the shunt is created by placing a stent between the portal and hepatic venous circulation within the liver.

HEPATIC ENCEPHALOPATHY

- strict limitation of protein in diet (up to 40g/day) or total exclusion of protein
- Decrease of ammonia production in intestines:
  - Lactulose (Dufalak) 60-120ml/day orally
  - Rifaximin 1200mg/day, course 1-2 weeks **or** ciprofloxacin 500mg 2/d
- Increase of ammonia deactivation in liver and muscles:
  - Glutargin 50 ml + 150ml of 0,9%NaCl 2/day i/v dreep feed
  - Citrarginine 10ml 3/day orally

BLEEDING FROM VARICES

- Somatostatin 100mg every 2 hours during 2 days i/v
- Vasopressin 0,4 units/min, then 0,6-0,8 units/min i/v during 12-24 hr until bleeding is stopped
- Hemostatic therapy: aminocapronic acid 100ml i/v, ethamsilat 10ml i/v, vitamin K, plasma
- PPIs or H2blockers i/v
- Balloon tamponade
- Endoscopic treatment

- Surgical treatment (if conservative methods are ineffective)

LIVER TRANSPLANTATION is indicated for end-stage liver failure in suitable candidates.

THE DIFFERENTIAL DIAGNOSIS OF LC

The differential diagnosis of LC is performed with a number of diseases.

1. Liver cancer.
2. Liver echinococcosis.
3. Liver lues.
4. Budd- Chiari syndrome (progressive narrowing of hepatic veins).
5. Cruveilhier-Baumgarten syndrome (congenital anomaly of the umbilical vein).
6. Hepatolenticular degeneration (Wilson-Konovalov syndrome).

Liver cirrhosis. The control of an initial level of knowledge

1. Which of the listed below factors promote the development of liver cirrhosis?

   A. Viruses, alcohol abuse
   B. Bacteria, fungi
   C. Influence of vitamin supplements
   D. Rickettsia, mycoplasma
   E. Gallbladder diseases

2. What clinical symptoms are typical for the initial stage of liver cirrhosis?
   A. Nausea, vomiting, loss of body weight
   B. Loss of body weight, meteorism, feeling of heaviness in right hypochondrium
   C. Bitter taste in mouth, heartburn
   D. Enlargement of a liver, spleen, liver stigmata
   E. Xanthelasma, palmar erythema, ascitis

3. What causes the enlargement of a spleen in liver cirrhosis?
   A. Venous stasis
   B. Diffuse fibrosis of a red pulp
   C. Portal hypertension
   D. All of the mentioned above factors
   E. Increased number of arterio-venous shunts

4. What changes of CBC are typical for hypersplenism?
   A. Reduction of number of erythrocytes, thrombocytes , leukocytes
   B. Reduction of number of erythrocytes, leukocytes, increased number of thrombocytes
   C. Lymphocytosis, leucopenia
   D. Eosinopenia, increase of ESR
   E. Lymphocytosis, leukocytosis, reduction of eosinophils number

5. What changes in blood are the most typical for liver cirrhosis?
   A. Iron-deficiency anemia
   B. B12- folic acid deficiency anemia
   C. Hemolytic anemia
   D. None of the listed
   E. All of the listed

6. What influences the rise of the body temperature in liver cirrhosis?
   A. Inflammatory changes in hepatocytes
   B. Inflammation of bile ducts
   C. Associated gastroduodenitis
   D. Passage of pyrogenic intestinal flora through the liver
   E. Associated cholecystitis

7. What biochemical changes are typical for the syndrome of cytolisis?

   A. Increase of alkaline phosphatase, decrease of the common protein and cholesterol
   B. Decrease of iron content and prothrombin in the blood serum, increase of cholesterol

C. Increase of AST, ALT, LDG, bilirubin
D. Increase of bilirubin, alkaline phosphatase, prothrombin
E. Decrease of prothrombin and transaminases, increase of bilirubin

8. What biochemical changes are typical for the syndrome of cholestasis?
A. Increase of cholesterol and alkaline phosphatase, decrease of fibrinogen
B. Decrease of cholesterol and bile acids, increase of unconjugated bilirubin
C. Increase of cholesterol, alkaline phosphatase, the conjugated bilirubin
D. Decrease of the general bilirubin, cholesterol, increase of transaminases
E. Decrease of alkaline phosphatase, increase of ceruloplasmin and albumin

9. What are the findings on palpation when examining the patient with liver cirrhosis?
A. Enlarged, firm, rounded edge
B. Enlarged, doughy, rounded edge
C. Reduced, bumpy, pointy end
D. Enlarged, firm, pointy end
E. Reduced, doughy, rounded edge

10. The syndrome of a portal hypertension is?
A. Enlargement of a liver, meteorism, skin itch
B. Enlargement of a liver and a spleen, jaundice
C. Enlargement of a liver, ascites, varicose veins
D. Reduction of a liver, edemas, jaundice
E. Enlargement of a liver, ascitis, edemas, cardiomyopathy

Liver cirrhosis (the control of initial level of knowledge), correct answers:
1 A
2 B
3 D
4 A
5 C
6 D
7 C
8 C
9. D
10. C

Liver cirrhosis. The control of final level of knowledge

1. How many clinical stages are there in the course of hepatic coma?

A. 2
B. 3
C. 4
D. 1
E. None

2. What groups of medications are used for the treatment of liver cirrhosis?

A. Antibiotics, hepatoprotectors, vitamins
B. Hepatoprotectors, cytostatics, immunosuppressants
C. Hepatoprotectors,choleretics, spasmolytics
D. Hepatoprotectors, cholekinetics, anabolics
E. Sulfanilamides, hepatoprotectors , nitrates

3. What are the most informative methods for diagnosis of hepatic jaundice?

A. Biochemical blood assay
B. Duodenal probe
C. Cholecystography
D. Ultrasonography
E. Endoscopic retrograde pancreatocholangiography

4. What signs are the least typical for portal hypertension?

A. Development of collaterals
B. Hemorrhage from varicose veins
C. Ascites
D. Fever
E. Splenomegalia

5. The most probable sign of the hemorrhage from esophageal varices are:

A. Stomachache
B. Heartburn
C. Scarlet blood in emetic masses
D. Dark blood in emetic masses
E. Defecation of black color

6. The peculiarity of portal hypertension development in case of macronodular LC is:

A. It precedes the development of functional insufficiency of a liver
B. Occurs at exacerbation
C. Occurs early
D. Has stable course
E. All of the listed above are true

7. What medicines are prescribed for the treatment of ascites/edemas syndrome?

A. ACE inhibitors
B. Diuretics
C. Glucocorticoids
D. Interferons

8. Complications of LC include:

A. Chronic constipation
B. Acute intestinal impassability
C. Hepatic coma
D. An acute gastric hemorrhage
E. Chronic diarrhea

9. The leading clinical syndrome in macronodular LC is:

A. The syndrome of hepatic-cellular insufficiency
B. The syndrome of a portal hypertension
C. The syndrom of a jaundice and cholestasis
D. Asthenovegetative syndrome
E. Mesenchymal -inflammatory syndrome

10. The indication to application of glucocorticosteroids in LC is:

A. Mesenchymal-inflammatory syndrome
B. Splenomegalia
C. Hemorrhage from the varicose veins of a gullet
D. Marked asthenovegetative syndrome
E. Jaundice

Cirrhoses of a liver (the final level of knowledge)

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

Case-based questions.

1. The patient, who had suffered from LC for 5years, complaints on marked fatigue, skin pallor, cold sweats, thirst, vomiting with a touch of dark red blood. What is the most probable reason for occurrence of this type of hemorrhage?

A. Portal hypertension.
B. Thrombosis of hepatic veins
C. Malignization
D. Heart failure
E. Pulmonary embolism

2. The patient had been suffering from viral hepatitis B during past 4 years. He reports an alcohol abuse for many years. He complains on heartburn and burning pain behind the breastbone, which he has been feeling during the last 2 months. There was a vomiting with fresh dark blood in the morning after meals and lifting of weight. At examination – the skin is pale and wet, heartbeat rate - 92/min, BP 90/60 mm. Scleras are icteric, abdomen is enlarged due to ascites, hepatosplenomegalia. List the most probable reasons for the hemorrhage:

A. Achalasia of the esophagus
B. Malory-Weiss syndrome
C. Rupture of esophageal varices
D. Bud-Chiari syndrome
E. Duodenal ulcer

3. Patient with cirrhosis had recently complained on moderate pain in epigastrium, constant bloating, which increases after eating. Objective data: distended subcutaneous veins of abdomen, signs of free fluid in the abdomen, enlarged liver and spleen. Ultrasonography of abdomen: distention of portal vein, enlargement of liver and spleen. What kind of cirrhosis complication has developed in this patient?

A. Peritonitis
B. Dysbacteriosis
C. Portal hypertension
D. Hepatic failure
E. Thrombosis of a portal vein

4. Patient has micronodular liver cirrhosis. During last 2 months he noticed the development of dyspnea, edemas of lower extremities, ascites. Patient was taking hepatoprotectors and glucocorticoids. What combination of medicines should be added to the treatment, which is already conducted?

A. Spironolactone + ascorutine
B. Nerabol + furosemide
C. Lidokain + hydrochlorothiazide
D. Albumin + ascorutine
E. Spironolactone + furosemide

5. A 49 years old man is the handicapped person of the II group. He has been treated for liver cirrhosis for several years. During the last month his abdomen became noticeably enlarged, the general weakness has increased. During 2 weeks he has been taking furosemide on daily basis. He was directed to the hospital for treatment. What changes can be revealed in electrolyte blood assay?

A. Hypocalcemia
B. Hypokalemia
C. Hypernatremia
D. Hypercalcemia
E. Hypokalemia

6. A 46 years old man complains on vomiting containing bright red blood. He had been suffering from micronodular liver cirrhosis of viral etiology for 5 years. During last 6 months there is an enlargement of the abdomen due to ascites. What should be the first measure of the urgent therapy?

A. Vasopressin 20 units i/v
B. Cordiamin 2 ml. i/m
C. Mesatone 1 % - 2 ml i/m
D. Prednisolone 30 mg i/v
E. Swallowing pieces of ice.

7. A woman of 42 years old suffers from micronodular cryptogenic liver cirrhosis. During the last week her condition has worsened: there were cramps, dizziness, and increase of the jaundice. What laboratory assay should be done in order to explain the reason of deterioration of her condition?

A. Determination of ammonia level in serum.
B. Determination of cholesterol level in blood.
C. Determination of α-fetoprotein contents in blood
D. Determination of ALT and AST
E. Determination of alkaline phosphatase level

8. A patient with a background of liver cirrhosis, after the use of alcohol complains on headache, vomiting, disgust for meals, sleeplessness, jaundice, hepatic smell from a mouth, and bloating. What complication of liver cirrhosis has developed?

A. Hepatic failure
B. Hemorrhage from varices
C. Portal hypertension
D. Acute stomach ulcer
E. Mesenteric venous thrombosis

9. A patient, who had been suffering from LC for a long time, recently complains on the moderate pain in epigastrium, bloating after meals. Objective data: the distention of subcutaneous abdominal veins, the signs of a free liquid in the abdominal cavity, the enlargement of the liver and the spleen. Ultrasonography: distended portal vein, enlargement of liver and spleen. What is the most serious complication of LC in this patient?

A. Portal vein thrombosis
B. Hepatic failure
C. Portal hypertension
D. Peritonitis
E. Disbacteriosis of intestines

10. A woman of 24 years old complains on intensive skin itch, which worsens in the evenings and a dull pain in right side of the abdomen. She became sick 2 years ago after delivery. Objective data: jaundice, xanthelasmas on the eye lids. The liver is 6 cm enlarged above normal, dense, the edge is smooth, painless. The spleen is 3 cm enlarged above normal. The reaction to a superficial antigen of hepatitis B virus is negative. What form of a liver disease does the patient suffer from?

A. Fatty hepatosis

B. Chronic hepatitis
C. Chronic cholecystitis
D. Hemochromatosis
E. Primary biliary cirrhosis

Correct answers

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

Control questions.

1. Definition of LC.
2. The basic clinical syndromes of LC
3. The characteristics of biochemical syndromes of LC
4. The characteristics of physical data of LC.
5. The peculiarities of viral LC.
6. The peculiarities of toxic LC
7. Methods of diagnosis of LC.
8. Complications of LC.
9. Principles of treatment of viral LC
10. Principles of treatment of autoimmune LC
11. Lifestyle changes and diet in LC
12. Pharmacological therapy in LC
13. Prevention of LC

Practical tasks.

1. To supervise a patient with LC
2. To give interpretation for the laboratory assays.
3. To give interpretation for the insrtumental methods of study.
4. To perform differential diagnosis of LC
5. To list complications of LC
6. To write recipes concerning therapy of LC.

Further reading:

1. Beers MH, Berkow R, eds. Merck Manual Second Home Edition 2004–2005. "Clinical Manifestations of Liver Disease." Available at: http://www.merck.com/mmhe/sec10/ch135/ch135e.html?qt=portal%20hypertension&alt=sh.
2. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011 Mar;53(3):1020-2. doi: 10.1002/hep.24199.
3. Garcia-Tsao G, Lim JK; Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol* . 2009;104:1802-1829.
4. Heidelbaugh JJ, Bruderly M; Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006 Sep 1;74(5):756-62. [abstract]
5. Lochs H, Plauth M. Liver cirrhosis: rationale and modalities for nutritional support—the European Society of Parenteral and Enteral Nutrition consensus and beyond. *Curr Opin Clin Nutr Metab Care.* 1999;2:345–349.
6. Mehta G, Rothstein KD. Health maintenance issues in cirrhosis. *Med Clin North Am* . 2009;93:901-915.
7. Poynard T, Bedossa P, Opolon P; Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997 Mar 22;349(9055):825-32. [abstract]
8. Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology*. 1998;27:264–272.
9. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* . 2008;371:838-851.
10. Sherman M, Klein A; AASLD single-topic research conference on hepatocellular carcinoma: Conference proceedings. Hepatology. 2004 Dec;40(6):1465-73.