Міністерство охорони здоров'я України
Харківський національний медичний університет

Кафедра Внутрішньої медицини №3
Факультет VI по підготовці іноземних студентів

ЗАТВЕРДЖЕНО
на засіданні кафедри внутрішньої медицини №3
29 серпня 2016 р. протокол № 13
Зав. кафедри _____д.мед.н., професор Л.В. Журавльова

МЕТОДИЧНІ ВКАЗІВКИ
для студентів

з дисципліни «Внутрішня медицина (в тому числі з ендокринологією)
студенти 4 курсу I, II, III медичних факультетів, V та VI факультетів по підготовці іноземних студентів

Хронічні гепатити

Харків 2016

KHARKOV NATIONAL MEDICAL UNIVERSITY

DEPARTMENT OF INTERNAL MEDICINE N3

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

"Chronic hepatitis"

Kharkiv 2016

Practical class "Chronic hepatites (CH)", 4 hours

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 Obraztsov-Strazhesko;
4. Examination of skin and mucosa;
5. Physical data of liver examination.

Topic content

CHRONIC HEPATITIS

Chronic hepatitis (CH) represents a series of liver disorders of varying causes and severity in which

hepatic inflammation and necrosis continue for at least 6 months. Milder forms are nonprogressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis. Several categories of CH have been recognized. These include chronic viral hepatitis, drug-induced CH, and autoimmune CH. In many cases, clinical and laboratory features are insufficient to allow assignment into one of these three categories; these "idiopathic" cases are also believed to represent autoimmune CH. Finally, clinical and laboratory features of CH are observed occasionally in patients with such hereditary/metabolic disorders as Wilson's disease (copper overload), α1 antitrypsin deficiency, and nonalcoholic fatty liver disease and even occasionally in patients with alcoholic liver injury.

Classification of chronic hepatitis

Classification of CH is based on (1) its *cause*; (2) its histologic activity, or *grade*; and (3) its degree of progression, or *stage*. Thus, neither clinical features alone nor histologic features—requiring liver biopsy - alone are sufficient to characterize and distinguish among the several categories of CH.

By cause:

- chronic viral hepatitis, caused by hepatitis B, hepatitis B plus D, or hepatitis C
- autoimmune hepatitis, including several subcategories, I and II (perhaps III), based on serologic distinctions
- drug-associated chronic hepatitis
- category of unknown cause, or cryptogenic chronic hepatitis

By grade:

- mild
- moderate
- severe

Grade, a histologic assessment of necroinflammatory activity, is based on examination of the liver biopsy. An assessment of important histologic features includes the degree of *periportal necrosis* and the disruption of the limiting plate of periportal hepatocytes by inflammatory cells (so-called *piecemeal necrosis* or *interface hepatitis*); the degree of confluent necrosis that links or forms bridges between vascular structures - between portal tract and portal tract or even more important bridges between portal tract and central vein - referred to as *bridging necrosis*; the degree of hepatocyte degeneration and focal necrosis within the lobule; and the degree of *portal inflammation*. Several scoring systems that take these histologic features into account have been devised, and the most popular are the histologic activity index (HAI), used commonly in the United States, and the METAVIR score, used in Europe.

By stage:

The stage of CH, which reflects the level of progression of the disease, is based on the degree of hepatic fibrosis. When fibrosis is so extensive that fibrous septa surround parenchymal nodules and alter the normal architecture of the liver lobule, the histologic lesion is defined as *cirrhosis*. Staging is based on the degree of fibrosis as categorized on a numerical scale from 0−6 (HAI) or 0−4 (METAVIR).

Etiology

The most common causes are:

- Hepatitis B virus
- Hepatitis C virus
- Nonalcoholic steatohepatitis (NASH)
- Alcoholic hepatitis
- Idiopathic (probably autoimmune)

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) coinfection, and about 75% of cases of HCV infection become chronic. Rates are higher for HBV infection in children (eg, up to 90% of infected neonates and 30 to 50% of young children). Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.
Rarely, hepatitis E virus genotype 3 has been implicated in chronic hepatitis.
Hepatitis A virus does not cause chronic hepatitis.
Other causes of CH include nonalcoholic steatohepatitis (NASH) and alcoholic hepatitis. NASH develops most often in patients with at least one of the following risk factors:

- Obesity
- Dyslipidemia
- Glucose intolerance

Alcoholic hepatitis (a combination of fatty liver, diffuse liver inflammation, and liver necrosis) results from excess consumption.
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

Less common causes
Sometimes CH has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cholangitis). These conditions are called overlap syndromes.
Many drugs, including isoniazid, methyldopa, nitrofurantoin, and, rarely acetaminophen, can cause CH. The mechanism varies with the drug and may involve altered immune responses, cytotoxic intermediate metabolites, or genetically determined metabolic defects.
Less often, CH results from α1 antitrypsin deficiency, celiac disease, a thyroid disorder, hereditary hemochromatosis, or Wilson disease.

Clinical presentation

Clinical features of CH vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo.
Many patients are asymptomatic, especially in chronic HCV infection. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent.
Often, particularly with HCV, the first findings are:

- Signs of chronic liver disease (eg, splenomegaly, spider nevi, palmar erythema)
- Complications of cirrhosis (eg, portal hypertension, ascites, encephalopathy)

A few patients with CH develop manifestations of cholestasis (eg, jaundice, pruritus, pale stools, steatorrhea).
In autoimmune hepatitis, especially in young women, manifestations may involve virtually any

body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.
Chronic HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and, perhaps, non-Hodgkin B-cell lymphoma.
About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and rashes (urticaria, purpura, leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Diagnosis

- Liver function test results compatible with hepatitis (serum ALT, AST, alkaline phosphatase, and bilirubin)
- Viral serologic tests
- Possibly autoantibodies, immunoglobulins, alpha-1 antitrypsin level, and other tests
- Usually biopsy
- Serum albumin, platelet count, and prorhrombin time/international normalized ratio

The diagnosis is suspected in patients with any of the following:

- Suggestive symptoms and signs
- Incidentally noted elevations in aminotransferase levels
- Previously diagnosed acute hepatitis

Liver function tests. Aminotransferase elevations are the most characteristic laboratory abnormalities. Although levels can vary, they are typically 100 to 500 IU/L. ALT is usually higher than AST. Aminotransferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV. Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high. Bilirubin is usually normal unless the disease is severe or advanced.
However, abnormalities in these laboratory tests are not specific and can result from other disorders, such as alcoholic liver disease, recrudescent acute viral hepatitis, and primary biliary cirrhosis.

Other laboratory tests
If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV. Unless these tests indicate viral etiology, further testing is required.
The next tests done include:

- Autoantibodies (antinuclear antibody, anti–smooth muscle antibody, antimitochondrial antibody, liver-kidney microsomal antibody)
- Immunoglobulins
- Thyroid tests (thyroid-stimulating hormone)
- Tests for celiac disease (tissue transglutaminase antibody)
- Alpha-1 antitrypsin level
- Iron and ferritin levels and total iron-binding capacity

Children and young adults are screened for Wilson disease by measuring the ceruloplasmin level.
Marked elevations in serum immunoglobulins suggest chronic autoimmune hepatitis but are not conclusive.
Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti–smooth muscle (ASMA), or anti-liver/kidney microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children).Antimitochondrial antibodies are occasionally present in patients with autoimmune hepatitis.
Serum albumin, platelet count, and PT should be measured to determine severity; low serum albumin, a low platelet count, or prolonged PT may suggest cirrhosis and even portal hypertension.

Biopsy
Unlike in acute hepatitis, biopsy is necessary.
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.
Biopsy is also used to grade and stage the disease.
In most cases, the specific cause of CH 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.

Screening for complications
If symptoms or signs of cryoglobulinemia develop during CH, particularly with HCV, cryoglobulin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.
Patients with chronic HBV infection should be screened every 6 month for hepatocellular cancer with ultrasonography and serum alpha-fetoprotein measurement, although the cost-effectiveness of this practice is debated. Patients with chronic HCV infection should be similarly screened only if advanced fibrosis or cirrhosis is present.

Prognosis

Prognosis is highly variable.
Chronic hepatitis caused by a drug often regresses completely when the causative 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). Coinfection 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 causes cirrhosis in 20 to 30% of patients, although development may take decades and varies because it is often related to a patient's other risk factors for chronic liver disease, including alcohol use and obesity.
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 or advanced fibrosis has developed.

Treatment

- Supportive care
- Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV and HCV infection)

There are specific antiviral treatments for chronic hepatitis B (eg, entecavir and tenofovir as first-line therapies) and antiviral treatments for chronic hepatitis C (eg, interferon-free regimens of direct-acting antivirals).
General treatment
Treatment goals for chronic hepatitis include treating the cause and managing complications (eg,

ascites, encephalopathy) if cirrhosis and portal hypertension have developed.
Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson disease, should be treated.
In chronic hepatitis due to HBV, prophylaxis (including immunoprophylaxis) for contacts of patients may be helpful. No vaccination is available for contacts of patients with HCV infection.
Corticosteroids and immunosuppressants should be avoided in chronic hepatitis B and C because these drugs enhance viral replication. If patients with chronic hepatitis B require treatment with corticosteroids, immunosuppressive therapies, or cytotoxic chemotherapy for other disorders, they should be treated with antiviral drugs at the same time to prevent a flare-up of acute hepatitis B or acute liver failure due to hepatitis B. A similar situation with hepatitis C being activated or causing acute liver failure has not been described.
Treatment of NASH aims to:

- Eliminate causes
- Control risk factors for NASH

It may involve recommending weight loss, treating hyperlipidemias and hyperglycemia, stopping drugs associated with NASH (eg, amiodarone, tamoxifen, methotrexate, corticosteroids such as prednisone or hydrocortisone, synthetic estrogens), and avoiding exposure to toxins (eg, pesticides).
Autoimmune hepatitis - corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 60 mg po once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. To prevent long-term need for corticosteroid treatment, clinicians can transition to azathioprine 1 to 1.5 mg/kg po once/day or mycophenolate mofetil 1000 mg twice/day after corticosteroid induction is complete and then gradually taper the corticosteroid. Most patients require long-term, low-dose, corticosteroid-free maintenance treatment.
Liver transplantation may be required for decompensated cirrhosis.

CHRONIC VIRAL HEPATITIS

- Defined by chronic infection (HBV, HCV, HDV) for 3–6 months.
- Diagnosis is usually made by antibody tests and viral nucleic acid in serum.

Chronic hepatitis B afflicts nearly 400 million people worldwide (endemic areas include Asia and sub-Saharan Africa). It may be noted as a continuum of acute hepatitis B or diagnosed because of repeated detection of HBsAg in serum, often with elevated aminotransferase levels.
Four phases of HBV infection are recognized:

- **immune tolerant phase,** HBeAg and HBV DNA are present in serum, which is indicative of active viral replication, and serum aminotransferase levels are normal, with little necroinflammation in the liver.
- **immune clearance phase,** in which aminotransferase levels are elevated and necroinflammation is present in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of > 2% per year in those with cirrhosis); low-level IgM anti-HBc is present in serum in about 70%.
- patients enter the **inactive HBsAg carrier state** when biochemical improvement follows immune clearance. This improvement coincides with disappearance of HBeAg and reduced HBV DNA levels (10^5 copies/mL, or 20,000 international units/mL) in serum, appearance of anti-HBe, and integration of the HBV genome into the host genome in infected hepatocytes. Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and hepa- tocellular carcinoma.
- The **reactivated chronic hepatitis B phase** may result from infection by a pre-core mutant of HBV or spontaneous mutation of the pre-core or core promoter region of the HBV genome during the course of CH caused by wild-type HBV. So-called HBeAg-negative chronic hepatitis B accounts for 10% of cases of chronic hepatitis B in the United States, up to 50%

in southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8–10% per year)

Treatment. Patients with active viral replication (HBeAg and HBV DNA [10^5 copies/mL, or 20,000 international units/mL] in serum and elevated aminotransferase levels) may be treated with a nucleoside or nucleotide analog or with pegylated interferon. Nucleoside and nucleotide analogs - entecavir, tenofovir, lamivudine, adefovir, and telbivudine - are preferred because they are better tolerated and can be taken orally. First-line treatment is usually with an oral antiviral drug, such as entecavir (a nucleoside analog) or tenofovir (a nucleotide analog). For patients who are HBeAg-negative, the threshold for treatment is a serum HBV DNA level 10^4 copies/mL, or 2000 international units/mL. If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients over age 35–40 if liver biopsy demonstrates a fibrosis stage of 2 (moderate) or higher. Therapy is aimed at reducing and maintaining the serum HBV DNA level to the lowest possible levels, thereby leading to normalization of the ALT level and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and some responders eventually clear HBsAg. Although nucleoside and nucleotide analogs generally have been discontinued 6–12 months after HBeAg-to-anti-HBe seroconversion, some patients serorevert to HBeAg after discontinuation, have a recurrence of hepatitis activity, and require long-term therapy, which also is required when seroconversion does not occur. All HBeAg-negative patients with chronic hepatitis B also require long-term therapy.

Acute ***hepatitis D*** infection superimposed on chronic HBV infection may result in severe CH, which may progress rapidly to cirrhosis and may be fatal. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular carcinoma. The diagnosis is confirmed by detection of anti-HDV or HDAg (or HDV RNA) in serum.
Peginterferon alfa-2b (1.5 mcg/kg/wk for 48 weeks) may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20–50% of patients with **chronic hepatitis D,** but patients may relapse and tolerance is poor. Nucleoside and nucleotide analogs are not effective in treating chronic hepatitis D.

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. It is clinically indistinguishable from CH due to other causes and may be the most common. Worldwide, 170 million people are infected with HCV. In approximately 40% of cases, serum aminotransferase levels are persistently normal. The diagnosis is confirmed by detection of anti-HCV by EIA. In rare cases of suspected chronic hepatitis C but a negative EIA, HCV RNA is detected by polymerase chain reaction testing. Progression to cirrhosis occurs in 20% of affected patients after 20 years, with an increased risk in men, those who drink more than 50 g of alcohol daily, and those who acquire HCV infection after age 40 years. The rate of fibrosis progression accelerates after age 50. African Americans have a higher rate of chronic hepatitis C but lower rates of fibrosis progression and response to therapy than whites. Immunosuppressed persons— including patients with hypogammaglobulinemia, HIV infection with a low CD4 count, or those receiving immunosuppressants—appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco and cannabis smoking and hepatic steatosis also appear to promote progression of fibrosis, but coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild CH with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients.
Treatment

- Direct-acting antiviral drugs
- Sometimes with pegylated interferon (IFN) and/or ribavirin

Treatment of chronic hepatitis C is generally considered in patients under age 70 with more than

mild fibrosis on liver biopsy. Because of high response rates to treatment in patients infected with HCV genotype 2 or 3, treatment may be initiated in these patients without a liver biopsy. The goal of treatment is permanent elimination of HCV-RNA, which is associated with permanent normalization of aminotransferase and cessation of histologic progression. Treatment results are more favorable in patients with moderate fibrosis and a viral load of < 600,000 to 800,000 IU/mL than in patients with cirrhosis and a viral load of > 800,000 IU/mL. Until late 2013, all genotypes were treated with pegylated IFN-alpha plus ribavirin. Now, most patients are treated with antiviral drugs (direct-acting antivirals [DAAs]) that affect specific HCV targets, such as proteases or polymerases.

DAAs used to treat HCV include:

- Telaprevir and boceprevir: 1st-generation protease inhibitors with activity against HCV genotype 1
- Simeprevir: A 2nd-generation genotype 1–specific protease inhibitor
- Sofosbuvir: A polymerase inhibitor with activity against HCV genotypes 1 to 6
- Paritaprevir: A protease inhibitor
- Ledipasvir: A protease inhibitor
- Dasabuvir: A polymerase inhibitor
- Ombitasvir: An inhibitor of the viral nonstructural protein 5A (NS5A inhibitor)
- Daclatasvir: An NS5A inhibitor
- Elbasvir: An NS5A inhibitor
- Grazoprevir: A protease inhibitor

Telaprevir, boceprevir, and simeprevir are given with pegylated IFN and ribavirin.

Sofosbuvir can be used without interferon; it can be given with ribavirin (for genotypes 1 to 6), simeprevir (for genotype 1), or daclatasvir (for genotypes 1 to 3) in all-oral regimens. Ledipasvir and sofosbuvir are available in a single pill to treat HCV genotypes 1, 4, and 6. Elbasvir/grazoprevir in a single pill is used to treat HCV genotypes 1 and 4.

The following 5-drug regimen is effective against genotypes 1 and 4:

- Paritaprevir/ ritonavir/ombitasvir (in a single pill) given once/day
- Dasabuvir, given twice/day
- Ribavirin, given twice/day

Paritaprevir/ritonavir/ombitasvir plus dasabuvir are available in a single package.

Ritonavir increases levels of paritaprevir but has no direct antiviral activity. Ribavirin is often used with DAAs.

AUTOIMMUNE HEPATITIS

- Usually young to middle-aged women.
- Chronic hepatitis with high serum globulins and characteristic liver histology.
- Positive antinuclear antibody (ANA) and/or smooth muscle antibody in most common type.
- Responds to corticosteroids.

Although autoimmune hepatitis is usually seen in young women, it can occur in either sex at any age. The incidence and prevalence are estimated to be 8.5 and 107 per million population, respectively. Affected younger persons are often positive for HLA-B8 and HLA-DR3; older patients are often positive for HLA-DR4.

The onset is usually insidious, but up to 40% of cases present with an acute (occasionally fulminant) attack of hepatitis and some cases follow a viral illness (such as hepatitis A, Epstein-Barr infection, or measles) or exposure to a drug or toxin (such as nitrofurantoin, minocycline, or infliximab). Exacerbations may occur postpartum. 34% of patients are asymptomatic. Typically, examination reveals a healthy-appearing young woman with multiple spider nevi, cutaneous striae, acne, hirsutism, and hepatomegaly. Amenorrhea may be a presenting feature. Extrahepatic features include arthritis, Sjögren syndrome, thyroiditis, nephritis, ulcerative colitis, and Coombs-positive hemolytic anemia. Patients with autoimmune hepatitis are at increased risk for cirrhosis which, in

turn, increases the risk of hepatocellular carcinoma (at a rate of about 1% per year).

Treatment. Prednisone with or without azathioprine improves symptoms, decreases the serum bilirubin, aminotransferase, and γ-globulin levels and reduces hepatic inflammation. Symptomatic patients with aminotransferase levels elevated tenfold (or fivefold if the serum globulins are elevated at least twofold) are optimal candidates for therapy, and asymptomatic patients with modest enzyme elevations may be considered for therapy depending on the clinical circumstances and histologic severity. Prednisone is given initially in a dose of 30 mg orally daily with azathioprine, 50 mg orally daily, which is generally well tolerated and permits the use of lower corticosteroid doses than a regimen beginning with prednisone 60 mg orally daily alone. Preliminary experience suggests that budesonide, 6–9 mg orally daily, may be at least as effective as prednisone in noncirrhotic autoimmune hepatitis and associated with fewer side effects. The dose of prednisone is lowered from 30 mg/d after 1 week to 20 mg/d and again after 2 or 3 weeks to 15 mg/d. Ultimately, a maintenance dose of 10 mg/d is achieved. The response rate to therapy with prednisone and azathioprine is 80%. Nonresponders to corticosteroids and azathioprine (failure of serum aminotransferase levels to decrease by 50% after 6 months) may be considered for a trial of cyclosporine, tacrolimus, everolimus, methotrexate, or rituximab.

ALCOHOLIC LIVER DISEASE

- Chronic alcohol intake usually exceeds 80 g/d in men and 30–40 g/d in women with alcoholic hepatitis or cirrhosis.
- Fatty liver is often asymptomatic.
- Fever, right upper quadrant pain, tender hepatomegaly, and jaundice characterize alcoholic hepa- titis, but the patient may be asymptomatic.
- AST is usually elevated but usually not above 300 units/L; AST is greater than ALT, usually by a factor of 2 or more.
- Alcoholic hepatitis is often reversible but it is the most common precursor of cirrhosis

Excessive alcohol intake can lead to fatty liver, hepatitis, and cirrhosis. Alcoholic hepatitis is characterized by acute or chronic inflammation and parenchymal necrosis of the liver induced by alcohol. The frequency of alcoholic cirrhosis is estimated to be 10–15% among persons who consume over 50 g of alcohol daily for over 10 years. The risk of cirrhosis is lower (5%) in the absence of other cofactors such as chronic viral hepatitis and obesity. Women appear to be more susceptible than men, in part because of lower gastric mucosal alcohol dehydrogenase levels. Over 80% of patients with alcoholic hepatitis have been drinking 5 years or more before symptoms that can be attributed to liver disease develop; the longer the duration of drinking (10–15 or more years) and the larger the alcoholic consumption, the greater the probability of developing alcoholic hepatitis and cirrhosis. Deficiencies in vitamins and calories probably contribute to the development of alcoholic hepatitis and its progression to cirrhosis. Many adverse effects of alcohol on the liver are thought to be mediated by tumor necrosis factor and by the oxidative metabolite acetaldehyde, which contributes to lipid peroxidation and induction of an immune response following covalent binding to proteins in the liver.
The clinical presentation of alcoholic liver disease can vary from asymptomatic hepatomegaly to a rapidly fatal acute illness or end-stage cirrhosis. A recent period of heavy drinking, complaints of anorexia and nausea, and the demonstration of hepatomegaly and jaundice strongly suggest the diagnosis. Abdominal pain and tenderness, splenomegaly, ascites, fever, and encephalopathy may be present. Infection is common in patients with severe alcoholic hepatitis.

Treatment. Abstinence from alcohol is essential. Fatty liver is quickly reversible with abstinence. Every effort should be made to provide sufficient amounts of carbohydrates and calories in anorectic patients to reduce endogenous protein catabolism, promote gluconeogenesis, and prevent hypoglycemia. Nutritional support (40 kcal/kg with 1.5–2 g/kg as protein) improves liver disease,

but not necessarily survival, in patients with malnutrition. Methylprednisolone, 32 mg/d orally, or the equivalent, for 1 month, may reduce short-term mortality in patients with alcoholic hepatitis. Pentoxifylline—an inhibitor of tumor necrosis factor— 400 mg orally three times daily for 4 weeks, may reduce 1-month mortality rates in patients with severe alcoholic hepatitis, primarily by decreasing the risk of hepatorenal syndrome. It is often used when corticosteroids are contraindicated.

DRUG- & TOXIN-INDUCED LIVER DISEASE

- Drug-induced liver disease can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.
- Clinicians must inquire about the use of many widely used therapeutic agents, including over-the-counter "natural" and herbal products, in any patient with liver disease.

Many therapeutic agents may cause hepatic injury. The medications most commonly implicated are nonsteroidal anti-inflammatory drugs and antibiotics because of their widespread use. In any patient with liver disease, the clinician must inquire carefully about the use of potentially hepatotoxic drugs or exposure to hepatotoxins, including over-the-counter "natural" and herbal products. In some cases, coadministration of a second agent may increase the toxicity of the first (eg, isoniazid and rifampin, acetaminophen and alcohol). A relationship between increased serum ALT levels in premarketing clinical trials and postmarketing reports of hepatotoxicity has been identified. Except for drugs used to treat tuberculosis and HIV infection, the risk of hepatotoxicity is not increased in patients with preexisting cirrhosis. Drug toxicity may be categorized on the basis of pathogenesis or histologic appearance. Drug-induced liver disease can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.

NONALCOHOLIC FATTY LIVER DISEASE

- Often asymptomatic.
- Elevated aminotransferase levels and/or hepatomegaly.
- Macrovesicular and/or microvesicular steatosis with or without inflammation and fibrosis on liver biopsy.

Nonalcoholic fatty liver disease (NAFLD) is estimated to affect 20–45% of the population. Causes of NAFLD are obesity (present in 40%), diabetes mellitus (in 20%), hypertriglyceridemia (in 20%), corticosteroids, amiodarone, highly active antiretroviral therapy, toxins, endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypobetalipoproteinemia and other metabolic disorders, obstructive sleep apnea, excessive dietary fructose consumption, starvation and refeeding syndrome, and total parenteral nutrition. Genetic factors are likely to play a role. Steatosis is nearly universal in obese alcoholic patients and is a hallmark of insulin resistance (metabolic syndrome), which is characterized by obesity, diabetes, hypertriglyceridemia, and hypertension. The risk of fatty liver in persons with meta- bolic syndrome is 4 to 11 times higher than that of persons without insulin resistance. Physical activity protects against the development of NAFLD. In addition to macrovesicular steatosis, histologic features may include focal infiltration by polymorphonuclear neutrophils and Mallory hyalin, a picture indistinguishable from that of alcoholic hepatitis and referred to as nonalcoholic steatohepatitis (NASH), which affects 3–5% of the population. In patients with NAFLD, older age, obesity, and diabetes mellitus are risk factors for advanced hepatic fibrosis and cirrhosis. Cirrhosis caused by NASH appears to be uncommon in African Americans.
Most patients with NAFLD are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver dis- ease are uncommon.

Treatment. Treatment consists of removing or modifying the offending factors. Weight loss,

dietary fat restriction, and exercise (through reduction of abdominal obesity) often lead to improvement in liver biochemical tests and steatosis in obese patients with NAFLD.

Clinical and laboratory features of chronic hepatitis

Type of Hepatitis	Diagnostic Test(s)	Autoantibodies	Therapy
Chronic hepatitis B	HBsAg, IgG anti-HBc, HBeAg, HBV DNA	Uncommon	IFN-α, PEG IFN-α Oral agents: First-line: entecavir, tenofovir Second-line: lami-vudine, adefovir, telbivudine
Chronic hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1[a]	PEG IFN-α plus ribavirin Telaprevir[b] Boceprevir[b] Simeprevir[b] Sofosbuvir[b]
Chronic hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3	IFN-α, PEG IFN-α[c]
Autoimmune hepatitis	ANA[d] (homogeneous), anti-LKM1 (±) Hyperglobulinemia	ANA, anti-LKM1 anti-SLA[e]	Prednisone, azathioprine
Drug- associated	-----	Uncommon	Withdraw drug
Cryptogenic	All negative	None	Prednisone (?), azathioprine (?)

[a]Antibodies to liver-kidney microsomes type 1 (autoimmune hepatitis type II and some cases of hepatitis C).

[b]Administered as a triple-drug combination with PEG IFN and ribavirin.

[c]Early clinical trials suggested benefit of IFN-α therapy; PEG IFN-α is as effective, if not more so, and has supplanted standard IFN-α.

[d]Antinuclear antibody (autoimmune hepatitis type I).

[e]Antibodies to soluble liver antigen (autoimmune hepatitis type III).

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. Concomitatnt 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 * 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. essentiale forte

5. Student, 20, was on outpatient treatment for 3 days due to respiratory infection and an increase of body temperature up to 38º 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 aminotranspherase 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 * 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 mlmol / 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 38ºC. 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.

Clinical examination of the patient

Name of the patient_____

Age____profession_____

Complaints_____

Anamnesis morbi

_____

Anamnesis vitae

_____

The results of physical examination of the patient:

_____

Preliminary diagnosis:

_____
_____
_____
_____

The results of additional research methods:

_____
_____
_____
_____
_____
_____
_____

Substantiation of clinical diagnosis:

_____
_____
_____
_____
_____
_____
_____

Clinical diagnosis:

Main diagnosis_____
_____
_____

Concomitant pathology

_____
_____
_____
_____

Complications

_____
_____
_____
_____

Treatment:

1. _____

2. Diet _____

3._____

4._____

5. _____

Further reading:

1. Davidson's "Principles and Practice of Medicine" 21st edition, Alimentary tract and pancreatic disease, p. 835-919.
2. Current Medical Diagnosis and Treatment, Gastrointestinal disorders, 2014, p. 564-662
3. Harrison's, Principles of Internal Medicine, 19th edition, Gastoenterology and Hepatology, p.257-398
4. The Mercks Manual for healthcare professionals http://www.merckmanuals.com
5. Kasper D.L., Fauci A.S., Longo D.L, et al: Harrison's principles of internal medicine. 16th edition. 2005.
6. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol*. Dec 2008;6(12):1315-41; quiz 1286.
7. Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology*. May 2009;49(5 Suppl):S72-84.
8. Previsani N, Lavanchy D. World Health Organization. Hepatitis C (WHO/CDS/CSR/LYO/2003.). 2002.
9. Previsani N, Lavanchy D. World Health Organization. Hepatitis D. (WHO/CDS/CSR/NCS/2001.1). 2001.
10. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. Aug 13 2011;378(9791):571-83.
11. Krawitt EL. Autoimmune hepatitis: classification, heterogeneity, and treatment. *Am J Med*. Jan 17 1994;96(1A):23S-26S.
12. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol*. Dec 1995;19(12):1409-17.
13. Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology*. May 2009;49(5 Suppl):S122-8.
14. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. Apr 2009;49(4):1335-74.

Інформаційні ресурси

сайт кафедри внутрішньої медицини № 3 ХНМУ http://www. vnmed3.kharkiv.ua/, встановлене інформаційно-освітнє середовище Moodle на піддомен сайта http://distance-training. vnmed3.kharkiv.ua

Методична вказівка складена: асистентом А.К. Журавльовою

Методична вказівка переглянута і затверджена на засіданні кафедри: _____

З доповненнями (змінами) _____

Завідувач кафедри Л.В. Журавльова