Ministry of Healthcare of Ukraine
Poltava State Medical University

**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

Academic discipline	Internal medicine
Module	Current practice of internal medicine
Content module	Management of the patients with main symptoms and syndromes in gastroenterology clinic
Study subject	**Management of patients with hepatomegaly and hepatolienal syndrome**
Course	VI
Faculty	of foreign students training

1. **Relevance of the topic**: Hepatomegaly is the condition of having an enlarged liver. It is a non-specific medical sign having many causes, which can broadly be broken down into infection, hepatic tumours, or metabolic disorder. Often, hepatomegaly will present as an abdominal mass. Depending on the cause, it may sometimes present along with jaundice.Congestive splenomegaly is common in patients with portal hypertension.

2. **The main goal:** To be able to choose and put into practice the approach to the patient with hepatomegaly and hepatolienal syndrome, to put diagnosis and to determine tactics of treatment and prophylaxis.

Specific goals:

- To select the information indicating the cause of hepatomegaly and hepatolienal syndrome;
- To create a scheme of diagnostic search;
- To identify the other signs of diseases that runs with hepatomegaly and hepatolienal syndrome (general examination, palpation, percussion, auscultation);
- To analyze and interpret the changes in the results of the laboratory and instrumental methods of investigation, depending on the course of the disease;
- To formulate and justify a preliminary diagnosis according to modern classifications;
- To conduct differential diagnostics of diseases with the hepatomegaly and hepatolienal syndrome;
- To develop a strategy of treatment depending on the disease and the existing complications;
- To provide medical care;
- To assess the patient's prognosis and to propose a plan of preventive actions;
- To apply deontological communication skills with patients.

3. **Basic knowledge, abilities, skills (interdisciplinary integration)**

Discipline	To know	To be able to
Anatomy	The structure of the gastrointestinal tract, blood supply, innervation	
Histology	The structure of the esophagus, stomach, intestines, liver, gallbladder, pancreas in health and disease	To interpret results of endoscopy, USI and biopsy
Regional anatomy	Interposition of the gastrointestinal organs	
Physiology	Indicators of gastrointestinal tract function, its value	To determine the function of gastrointestinal organs
Morbid anatomy	Changes in the structure of gastrointestibal tract organs in pathology	
Radiology	Radiological changes at pathology of gastrointestinal organs	Analyze the radiological picture of the chest cavity and abdominal cavity
Propaedeutic therapy	Diseases with abdominal pain as leading symptom	Perform an objective examination of the patient, analyze the clinical and laboratory results
Pharmacology	The mechanism of action,	Prescribe the drugs of these groups

	indications and contraindications for the IPP, H2-blockers, antacids, prokinetics, antibiotics, enzymes, pain killers, antispasmodics	

4. Do the tasks for independent work during preparation for classes.

4.1. The list of key terms, parameters, characteristics:

Term	Definition
Chronic hepatitis	are liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months.
Syndrome of cytolysis	complex of symptoms that includes clinical signs and elevated liver intracellular enzymes (AST, ALT, GDG, LDG) in blood that indicates on necrosis.
Syndrome of cholestasis	complex of symptoms that includes jaundice, skin itching, dark urine, light-colored stool and elevated GGTP, alkaline phosphatase, cholesterol, direct and total bilirubin in blood serum.
Steatosis	is the accumulation of triglycerides in hepatocytes.
Liver cirrhosis	is a diffuse process characterized by fibrosis and conversion of normal architecture to structurally abnormal nodules.

4.2. Theoretical questions for the lesson:

1. Give the definitions of hepatomegaly and hepatolienal syndrome, name and define diseases which are characterized by abdominal pain.

2. Specify the risk factors for diseases that lead to hepatomegaly and hepatolienal syndrome.

3. The pathophysiological mechanisms of hepatomegaly and hepatolienal syndromein different pathologies.

4. Diagnostic criteria of hepatitis and liver cirrhosis.

5. Modern classifications ofhepatomegaly and hepatolienal syndrome.

6. Specify the principles and features of hepatomegaly and hepatolienal syndrome pharmacotherapy according to modern recommendations depending on etiological factor.

7. What lifestyle modifications should be recommended for patients with hepatomegaly and hepatolienal syndrome according to reason?

4.3. Practical tasks that are performed in class:

1. What laboratory test can give the most precise characteristic of cytolysis degree?

1) **Transaminase test**
2) Weltman's coagulation test
3) Takata-Ara test
4) Prothrombin test
5) Test for whole protein

2. What preparations will be the most effective in viral hepatitis?

1) Antibiotics

2) Glucocorticoids

3) Hepatoprotectors

4) Alpha-interferon

5) Lactulose

3. What method of diagnostics will be the most informative in detecting the etiology of hepatitis?

1) Proteinogram

2) Markers of viral hepatitis

3) Violation of cellular immunity

4) Activity of cytolysis (AST, ALT)

5) Puncture biopsy of liver

4. What is the most effective treatment of autoimmune hepatitis?

1) Antibacterial preparations

2) Glucocorticoids, cytostatic preparations

3) Hepatoprotector preparations

4) Antiviral preparations

5) Hemosorbtion, vitaminotherapia

5. Presence of the antibodies to smooth muscle cells may indicate on:

1) Autoimmune hepatitis

2) Primary biliary cirrhosis

3) Gilbert's syndrome

4) Cholangiogenic hepatitis

5) Hemachromatosis

6. The two main consequences of cirrhosis are:

1) Encephalopathy and splenomegaly

2) Hepatomegaly and splenomegaly

3) Hepatocellular carcinoma and ascites

4) Anaemia and thrombocytopenia

5) Portal hypertension and liver insufficiency

7. What preparations will be the most effective in viral cirrhosis?

1) Antibiotics

2) Glucocorticoids

3) Hepatoprotectors

4) Alpha-interferon

5) Lactulose

8. What method of diagnostics will be the most informative in detecting liver cirrhosis?

1) Proteinogram

2) Markers of viral hepatitis

3) Violation of cellular immunity

4) Activity of cytolysis (AST, ALT)

5) Puncture biopsy of liver

9. Toreduce portal pressure can be used:

1) Diuretics

2) Antibiotics

3) Nonselective beta-blockers

4) Antifibrotics

5) Lactulose

10. What laboratory test can give the most precise characteristic of cytolysis degree?

1) Transaminase test

2) Weltman's coagulation test

3) Takata-Ara test

4) Prothrombin test

5) Test for whole protein

Topic Content

HEPATOMEGALY AND HEPATOLIENAL SYNDROME

Congestive splenomegaly is common in patients with portal hypertension. Clinical features include the presence of an enlarged spleen on physical examination and the development of thrombocytopenia and leukopenia in patients who have cirrhosis. Some patients will have fairly significant left-sided and left upper quadrant abdominal pain related to an enlarged and engorged spleen. Splenomegaly itself usually requires no specific treatment, although splenectomy can be successfully performed under very special circumstances.

Hypersplenism with the development of thrombocytopenia is a common feature of patients with cirrhosis and is usually the first indication of portal hypertension.

The most common symptoms produced by diseases involving the spleen are pain and a heavy sensation in the LUQ. Massive splenomegaly may cause early satiety. Pain may result from acute swelling of the spleen with stretching of the capsule, infarction, or inflammation of the capsule.

A palpable spleen is the major physical sign produced by diseases affecting the spleen and suggests enlargement of the organ. The normal spleen weighs <250 g, decreases in size with age, normally lies entirely within the rib cage, has a maximum cephalocaudad diameter of 13 cm by ultrasonography or maximum length of 12 cm and/or width of 7 cm by radionuclide scan, and is usually not palpable.

For bimanual palpation, which is at least as reliable as the other techniques, the patient is supine with flexed knees. The examiner's left hand is placed on the lower rib cage and pulls the skin toward the costal margin, allowing the fingertips of the right hand to feel the tip of the spleen as it descends while the patient inspires slowly, smoothly, and deeply. Palpation is begun with the right hand in the left lower quadrant with gradual movement toward the left costal margin, thereby identifying the lower edge of a massively enlarged spleen. When the spleen tip is felt, the finding is recorded as centimeters below the left costal margin at some arbitrary point, i.e., 10–15 cm, from the midpoint of the umbilicus or the xiphisternal junction. This allows other examiners to compare findings or the initial examiner to determine changes in size over time. Bimanual palpation in the right lateral decubitus position adds nothing to the supine examination. Percussion for splenic dullness is accomplished with any of three techniques described by Nixon, Castell, or Barkun:

1. Nixon's method: The patient is placed on the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in the

posterior axillary line and proceeds diagonally along a perpendicular line toward the lower midanterior costal margin. The upper border of dullness is normally 6–8 cm above the costal margin. Dullness >8 cm in an adult is presumed to indicate splenic enlargement.

2. Castell's method: With the patient supine, percussion in the lowest intercostal space in the anterior axillary line (eighth or ninth) produces a resonant note if the spleen is normal in size. This is true during expiration or full inspiration. A dull percussion note on full inspiration suggests splenomegaly.

3. Percussion of Traube's semilunar space: The borders of Traube's space are the sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. The patient is supine with the left arm slightly abducted. During normal breathing, this space is percussed from medial to lateral margins, yielding a normal resonant sound. A dull percussion note suggests splenomegaly. Studies comparing methods of percussion and palpation with a standard of ultrasonography or scintigraphy have revealed sensitivity of 56–71% for palpation and 59–82% for percussion. Reproducibility among examiners is better for palpation than percussion. Both techniques are less reliable in obese patients or patients who have just eaten.

Thus, the physical examination techniques of palpation and percussion are imprecise at best. It has been suggested that the examiner perform percussion first and, if positive, proceed to palpation; if the spleen is palpable, then one can be reasonably confident that splenomegaly exists. However, not all LUQ masses are enlarged spleens; gastric or colon tumors and pancreatic or renal cysts or tumors can mimic splenomegaly. The presence of an enlarged spleen can be more precisely determined, if necessary, by liver-spleen radionuclide scan, CT, MRI, or ultrasonography. The latter technique is the current procedure of choice for routine assessment of spleen size (normal = a maximum cephalocaudad diameter of 13 cm) because it has high sensitivity and specificity and is safe, noninvasive, quick, mobile, and less costly. Nuclear medicine scans are accurate, sensitive, and reliable but are costly, require greater time to generate data, and use immobile equipment. They have the advantage of demonstrating accessory splenic tissue. CT and MRI provide accurate determination of spleen size, but the equipment is immobile and the procedures are expensive. MRI appears to offer no advantage over CT. Changes in spleen structure such as mass lesions, infarcts, inhomogeneous infiltrates, and cysts are more readily assessed by CT, MRI, or ultrasonography. None of these techniques is very reliable in the detection of patchy infiltration (e.g., Hodgkin's disease).

Diseases associated with splenomegaly are are grouped according to the presumed basic mechanisms responsible for organ enlargement and need performing of differential diagnosis:

1. Hyperplasia or hypertrophy related to a particular splenic function such as reticuloendothelial hyperplasia (work hypertrophy) in diseases such as hereditary spherocytosis or thalassemia syndromes that require removal of large numbers of defective red blood cells; immune hyperplasia in response to systemic infection (infectious mononucleosis, subacute bacterial endocarditis) or to immunologic diseases (immune thrombocytopenia, SLE, Felty's syndrome).

2. Passive congestion due to decreased blood flow from the spleen in conditions that produce portal hypertension (cirrhosis, BuddChiari syndrome, congestive heart failure).

3. Infiltrative diseases of the spleen (lymphomas, metastatic cancer, amyloidosis, Gaucher's disease, myeloproliferative disorders with extramedullary hematopoiesis). The differential diagnostic possibilities are much fewer when the spleen is ―massively enlarged,‖ palpable more than 8 cm below the left costal margin or has a drained weight of ≥1000 g (Table 79-3). The vast majority of such patients will have nonHodgkin's lymphoma, chronic

lymphocytic leukemia, hairy cell leukemia, chronic myeloid leukemia, myelofibrosis with myeloid metaplasia, or polycythemia vera.

The major laboratory abnormalities accompanying splenomegaly are determined by the underlying systemic illness. Erythrocyte counts may be normal, decreased (thalassemia major syndromes, SLE, cirrhosis with portal hypertension), or increased (polycythemia vera). Granulocyte counts may be normal, decreased (Felty's syndrome, congestive splenomegaly, leukemias), or increased (infections or inflammatory disease, myeloproliferative disorders). Similarly, the platelet count may be normal, decreased when there is enhanced sequestration or destruction of platelets in an enlarged spleen (congestive splenomegaly, Gaucher's disease, immune thrombocytopenia), or increased in the myeloproliferative disorders such as polycythemia vera. The CBC may reveal cytopenia of one or more blood cell types, which should suggest hypersplenism. This condition is characterized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. The latter characteristic is less precise because reversal of cytopenia, particularly granulocytopenia, is sometimes not sustained after splenectomy. The cytopenias result from increased destruction of the cellular elements secondary to reduced flow of blood through enlarged and congested cords (congestive splenomegaly) or to immune-mediated mechanisms. In hypersplenism, various cell types usually have normal morphology on the peripheral blood smear, although the red cells may be spherocytic due to loss of surface area during their longer transit through the enlarged spleen. The increased marrow production of red cells should be reflected as an increased reticulocyte production index, although the value may be less than expected due to increased sequestration of reticulocytes in the spleen. The need for additional laboratory studies is dictated by the differential diagnosis of the underlying illness of which splenomegaly is a manifestation.

The main causes of hepatomegaly are chronic hepatitis of different etiologies and liver cirrhosis.

CHRONIC HEPATITIS

Definition. Chronic hepatitis 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. Finally, clinical and laboratory features of chronic hepatitis 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. Although all types of chronic hepatitis share certain clinical, laboratory, and histopathologic features, chronic viral and chronic autoimmune hepatitis are sufficiently distinct to merit separate discussions.

Classification. Chronic hepatitis includes chronic viral hepatitis, drug-induced chronic hepatitis, and autoimmune chronic hepatitis. 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 chronic hepatitis.

Common to all forms of chronic hepatitis are histopathologic distinctions based on localization and extent of liver injury. These vary from the milder forms, labeled chronic persistent hepatitis and chronic lobular hepatitis, to the more severe form, formerly called chronic active hepatitis. When first defined, these designations were believed to have prognostic implications, which were not corroborated by subsequent observations. Categorization of chronic hepatitis based primarily on histopathologic features has been replaced by a more informative

classification based on a combination of clinical, serologic, and histologic variables. Classification of chronic hepatitis is based on its cause; its histologic activity, or grade; and 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 chronic hepatitis.

By cause:

- viral hepatitis(hepatitis B, hepatitis B plus D, or hepatitis C);

- autoimmune hepatitis, including several subcategories, I and II and III, based on serologic distinctions;

- drug-associated chronic hepatitis;

- toxic (including alcohol);

- metabolic;

- unknown cause, or cryptogenic chronic hepatitis.

Non-alcoholic liver disease is also known as ―non-alcocholic steatohepatitis‖ can be related to chronic hepatitis.

By grade. 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.

Based on the presence and degree of these features of histologic activity, chronic hepatitis can be graded as mild, moderate, or severe.

By stage. The stage of chronic hepatitis, 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). Several noninvasive approaches have been introduced to provide approximations of hepatic histologic stage, including serum biomarkers of fibrosis (e.g. Fibro-test, Acti-test, Steato-test, Nash-test) and imaging determinations of liver elasticity.

Epidemiology. Chronic infection by hepatitis viruses is by far the main cause of chronic hepatitis worldwide, with more than 500 million individuals chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). Chronic viral hepatitis B and C are the leading cause of cirrhosis and hepatocellular carcinoma worldwide and account for more than 1 million deaths per year. Chronic HBV infection can be associated with infection by hepatitis D virus (HDV). Hepatitis A virus does not cause chronic hepatitis. Hepatitis E virus (HEV) does not cause chronic hepatitis, except rarely in patients who undergo liver transplantation.More than 350 million individuals, or 8.5% of the world's population, are chronic HBV carriers.HCV, which is present on all continents, is estimated to cause chronic infection in approximately 170 million individuals, or 3% of the world's population.Acute HCV infection evolves into chronic infection

in 50 to 80% of cases.HDV infection occurs only in HBsAg carriers. Only approximately 2% of patients acutely coinfected with HDV and HBV develop chronic hepatitis D.Autoimmune hepatitis typically presents between the ages of 15 and 25 years or between the ages of 45 and 60 years, and it is more common in women. Along with primary biliary cirrhosis and primary sclerosing cholangitis, autoimmune hepatitis is one of the three major autoimmune liver diseases. NAFLD has a prevalence ranging from 15 to 30% in the United States.The true prevalence of alcoholic liver disease is not known, but nearly 1% of North American adults are believed to have alcoholic liver disease.NAFLD is one of the most common causes of elevated liver enzymes and chronic liver disease in the Western world. Its incidence in adults and children is rising rapidly owing to the ongoing epidemics of obesity, type 2 diabetes mellitus, and metabolic syndrome. Its prevalence is quite high in certain patient populations; for example, nearly 80% of type 2 diabetic patients and 90% of morbidly obese individuals have imaging evidence of NAFLD.

Etiology and pathogenesis.*HBV* is not a cytopathic virus. Rather, liver injury in chronic hepatitis B is a consequence of the local immune response at the immune elimination phase. In particular, liver injury is related to cytotoxic T cells that recognize and kill infected hepatocytes that express HBV antigens at their surface and to the local production of cytokines. Chronic inflammation triggers fibrogenesis through the activation of hepatic stellate cells. The hepatitis B X protein may also directly activate fibrogenesis. As a result, many patients with chronic hepatitis B have progressive fibrosis, which may evolve into cirrhosis.

Chronic HCV infection is responsible for necroinflammatory lesions of varying severity, sometimes associated with steatosis, which is the accumulation of triglycerides in hepatocytes. HCV is not a cytopathic virus. Liver injury in chronic hepatitis C is related to the action of immune effectors that recognize and kill infected hepatocytes that express HCV antigens at their surface. Chronic inflammation triggers fibrogenesis through the activation of hepatic stellate cells. Fibrosis progresses at nonlinear rates that are generally faster in older patients, in males, and in the presence of chronic alcohol intake, viral coinfections, or immunosuppression. The severity of chronic hepatitis is independent of the HCV RNA level and of the HCV genotype. This chronic inflammation and progression of fibrosis predispose patients to cirrhosis and hepatocellular carcinoma.

Chronic hepatitis D is generally severe, with more than 80% of patients developing cirrhosis.

Autoimmune hepatitis is believed to be caused by autoimmune reactions against normal hepatocytes in genetically predisposed persons or persons exposed to unidentified triggers of an autoimmune process against liver antigens. Associations are seen with the human leukocyte antigen (HLA) class I B8 and class II DR3 and DR52a loci. In Asians, autoimmune hepatitis is associated with HLA DR4.

*Toxic hepatitis.*The liver is central to the metabolism of exogenous substances. Most drugs and xenobiotics cross the intestinal brush border because they are lipophilic. Biotransformation is the process by which lipophilic therapeutic agents are rendered more hydrophilic by the liver, resulting in drug excretion in urine or bile. In most instances, biotransformation changes a nonpolar to a polar compound through several steps. Foremost are oxidative pathways (e.g., hydroxylation) mediated by the cytochromes (CYPs) P-450. The next step is typically esterification to form sulfates and glucuronides, a process that results in the addition of highly polar groups to the hydroxyl group. These two enzymatic steps are referred to as phase I (CYP oxidation) and phase II (esterification). Other important metabolic pathways

involve glutathione-S-transferase, acetylating enzymes, and alcohol dehydrogenase, but the principal metabolic pathways for most pharmacologic agents involve CYPs and subsequent esterification.The exact details of the pathogenesis of liver injury are unclear for most drugs.Although most liver injury involves direct hepatocyte necrosis or apoptosis (hepatocellular injury), some drugs injure primarily the bile ducts or canaliculi and cause cholestasis without significant damage to hepatocytes. Other drugs affect sinusoidal cells or present a particular pattern of liver injury affecting multiple cell types (mixed type). Another approach to drug reactions emphasizes the histologic changes involved and the cell type.

REACTION TYPE	IMPLICATED DRUGS OR TOXINS
Autoimmune (attack on cell surface markers)	Lovastatin, methyldopa, nitrofurantoin
Cholestatic (attack on bile ducts)	Anabolic steroids, carbamazepine, chlorpromazine, estrogen, erythromycin
Fibrosis (activation of stellate cells leads to fibrosis)	Methotrexate, vitamin A excess
Granulomatous (macrophage stimulation)	Allopurinol, diltiazem, nitrofurantoin, quinidine, sulfa drugs
Hepatocellular (damage to smooth endoplasmic reticulum and immune cell surface)	Acetaminophen, Amanita poisoning, diclofenac, isoniazid, lovastatin, nefazodone, trazodone, venlafaxine
Immunoallergic (cytotoxic cell attack on surface determinants)	Halothane, phenytoin, sulfamethoxazole
Mixed (see above)	Amoxicillin-clavulanate, carbamazepine, cyclosporine, herbs, methimazole
Oncogenic (hepatic adenoma formation)	Oral contraceptives, androgenic agents
Steatohepatitis (mitochondrial dysfunction: β-oxidation and respiratory chain)	Amiodarone, perhexiline maleate, tamoxifen
Vascular collapse (ischemic damage)	Cocaine, ecstasy, nicotinic acid
Veno-occlusive disease (endotheliitis of sinusoidal endothelial cells)	Busulfan, cytoxan

Steatosis in the liver can be present in a microvesicular or macrovesicular pattern. Macrovesicular steatosis, the most common form, is characterized histologically by a single vacuole of fat filling up the hepatocyte and displacing the nucleus to the cell's periphery. Macrovesicular steatosis is typically caused by alcohol, diabetes, or obesity. Sometimes drugs such as corticosteroids or methotrexate may cause these hepatic changes. Amiodarone has been associated with a picture resembling alcoholic hepatitis, occasionally with progression to cirrhosis. The pathophysiology involves accumulation of phospholipids in the liver, eyes, thyroid, and skin. Treatment is primarily withdrawal of the drug and observation, although the half-life of amiodarone is prolonged.

In microvesicular steatosis, hepatocytes contain numerous small fat vesicles that do not displace the nucleus. These lesions are associated with disruption of mitochondrial DNA, resulting in anaerobic metabolism that leads to lactic acidosis in the most severe cases. Macrovesicular and microvesicular lesions may be observed concomitantly in some patients, and microvesicular lesions are more often associated with a poor prognosis. Hepatocellular necrosis may also be present. Acute fatty liver of pregnancy and Reye's syndrome are two examples of severe liver diseases caused by microvesicular steatosis.

*Nonalcoholic fatty liver disease*NAFLD is seen most commonly in obese, diabetic, and hyperlipidemic nonalcoholic patients. Not all obese patients have fatty liver disease, butNASH occurs in about 3 to 5% of the overweight and obese population, and liver fibrosis is increased in up to 40% of these individuals. Most patients with hepatic steatosis have stable, nonprogressive disease, but NASH can progress to cirrhosis. Many patients who were previously described as having cryptogenic cirrhosis are now thought to have NASH, especially because catabolic cirrhosis reduces macrovesicular steatosis, so late biopsy may show just a bland cirrhosis. Histologically, NAFLD resembles alcoholic liver disease, but it occurs in individuals without significant alcohol consumption. Average alcohol consumption greater than two drinks per day in men and greater than one drink per day in women generally is not consistent with a diagnosis of NAFLD. In addition, the definition of NAFLD excludes patients with a history of exposure to steatogenic medications such as amiodarone, methotrexate, and tamoxifen. NAFLD encompasses a spectrum of abnormal liver histology, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. In simple steatosis, liver histology reveals macrovesicular steatosis without ballooning degeneration of hepatocytes or liver fibrosis. NASH, which is a more advanced form of NAFLD, is histologically characterized by macrovesicular steatosis, ballooning degeneration of the hepatocytes, and sinusoidal fibrosis.

The major risk factors for NAFLD include obesity, type 2 diabetes mellitus, metabolic syndrome, and dyslipidemia. Other comorbidities associated with NAFLD include polycystic ovary syndrome, hypothyroidism, hypopituitarism, and sleep apnea. Two fundamental defects in NAFLD are insulin resistance/hyperinsulinemia and excessive levels of nonesterified fatty liver within the hepatocytes. An excessive influx of nonesterified fatty acids into the hepatocytes results in macrovesicular steatosis, which is predominantly centrilobular in location. Additionally, patients with NAFLD have increased de novo intrahepatic lipogenesis. Although patients with NAFLD robustly esterify free fatty acids in neutral triglycerides, free fatty acids within the hepatocytes are considered the primary mediators of cell injury (lipotoxicity). In the background of hepatic steatosis, factors that promote cell injury, inflammation, and fibrosis include oxidative stress, endoplasmic reticulum stress, apoptosis, adipocytokines, and stellate cell activation. The sources of oxidative stress include mitochondria and microsomes. Adipocytokines that play an important role in the pathogenesis of NAFLD include adiponectin and TNF-α. It is unclear why some patients with NAFLD exhibit NASH, whereas other patients with a comparable risk factor profile have only simple steatosis. There is a consistentand significant relationship of PNPLA3 genetic polymorphisms with the severity of steatosis and other histologic features of NAFLD. However, the genetic factors that play a role in NASH and NAFLD have not been fully elucidated.

Alcoholic fatty liver disease will develop in nearly 90% of individuals who consume alcohol heavily (on average, >6 drinks per day), and some individuals develop the more severe conditions of alcoholic hepatitis and alcoholic cirrhosis. The mechanisms underlying alcoholic liver injury can be broadly categorized into those caused by the effects of alcohol directly on hepatocytes and those caused by the effects mediated by Kupffer cells. The hepatocyte mechanisms include the altered redox state induced by alcohol and aldehyde dehydrogenase reactions, the oxidative stress and lipid peroxidation caused by the induction of CYP2E1 enzymes and the mitochondrial electron transfer system, and the effects of alcohol on the nuclear transcription factors (AMP kinase and SREBP-1c), protein adduct formation, and altered methionine and folate metabolism with resulting endoplasmic reticulum stress. Chronic alcohol consumption increases gut permeability, and the resulting portal endotoxemia activates Kupffer

cells. Activated Kupffer cells release a number of proinflammatory mediators, including tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), interleukins 1, 6, 8, and 10, and platelet-derived growth factor (PDGF). TNF-α has plethora of biologic effects and causes hepatocyte apoptosis, whereas TGF-β1 and PDGF play important roles in stellate cell activation, collagen production, and hepatic fibrosis. Among the known risk factors for developing alcoholic liver disease, the amount of alcohol consumed is the single most important. Forunclear reasons, only 30 to 35% of individuals with heavy and long-term drinking develop alcoholic hepatitis, and less than 20% develop cirrhosis. Women are at higher risk; for example, the risk of alcoholic cirrhosis increases after 10 years of alcohol consumption at quantities of more than 60 to 80 g/ day in men, whereas in women, it can develop at quantities of only more than 20 g/day. Moreover, the peak incidence of alcoholic liver disease in women is approximately a decade earlier than in men. The type of alcoholic beverage consumed may not be as critical, but —spirits‖ and beer may be more hepatotoxic than wine. African-American and Hispanic ethnic groups may be predisposed to more significant alcoholic liver injury. Both obesity and protein-calorie malnutrition, in which micronutrients and antioxidant capacity are diminished, also are important predispositions. Polymorphisms in genes associated with alcohol metabolism (alcohol and aldehyde dehydrogenases and cytochrome P-450 enzymes) and dysregulated cytokine production (e.g., TNF-α) may also influence genetic susceptibility. In patients with other forms of chronic liver disease (e.g., viral hepatitis B or C), concomitant alcohol consumption significantly aggravates liver injury.

Clinical features and diagnosis. The clinical symptoms of *chronic viral and autoimmune hepatitis*are typically nonspecific, and many patients have no symptoms. Fatigue, sleep disorders, and right upper quadrant pain may be present. Often the diagnosis is made when liver test abnormalities are identified by blood testing during a routine health evaluation or assessment for an unrelated problem or at the time of voluntary blood donation. More advanced symptoms include poorappetite, nausea, weight loss, muscle weakness, itching, dark urine, and jaundice. Patients can progress to full-blown cirrhosis, with its typical clinical manifestations. If cirrhosis is present, weakness, weight loss, abdominal swelling, edema, bruisability, gastrointestinal bleeding, and hepatic encephalopathy with mental confusion may arise. Other findings may include spider angiomas, palmar erythema, ascites, edema, and skin excoriations.

Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are usually two to five times the upper limit of normal. The ALT level is generally higher than the AST level, but both can be normal in mild or inactive disease or 10 to 25 times the upper limit of normal during acute exacerbations. Biologic tests can establish the specific diagnosis. Alkaline phosphatase and γ-glutamyl transpeptidase levels are usually minimally elevated unless cirrhosis is present. Serum bilirubin and albumin levels and the prothrombin time are normal unless the disease is severe or advanced. Serum immunoglobulin levels are mildly elevated or normal in chronic viral hepatitis but may be very elevated in autoimmune hepatitis. Results that suggest the presence of advanced fibrosis are a platelet count below 160,000, AST levels higher than ALT levels, elevation in serum bilirubin, decrease in serum albumin, prolongation of the prothrombin time, elevation in α-fetoprotein levels, and presence of rheumatoid factor or high globulin levels.

Serologic markers used to diagnose chronic hepatitis B include HBsAg, anti-HBs antibodies, total anti–hepatitis B core (HBc) antibodies and anti-HBc immunoglobulin M (IgM), HBeAg, and anti-HBe antibodies. Molecular markers include HBV DNA and HBV resistance substitutions; real-time polymerase chain reaction (PCR)–based assays are the best way to detect

and quantify HBV DNA. Chronic HBV infection is defined by the persistence of HBsAg in the serum for more than 6 months after the acute episode.

Chronic HCV infection is defined by the persistence of HCV RNA for more than 6 months. In patients with clinical and/or biologic signs of chronic liver disease, chronic hepatitis C is diagnosed by the simultaneous presence of anti-HCV antibodies and HCV RNA. Detectable HCV replication in the absence of anti-HCV antibodies is observed almost exclusively in patients who are profoundly immunosuppressed, on hemodialysis, or agammaglobulinemic. The HCV genotype, which has important therapeutic implications, should be determined. Anti-HCV IgM, which is found in about 50% of patients with chronic hepatitis, is of no significance.

Markers of HDV infection should be sought at least once in every chronic HBsAg carrier. Both total anti-HD antibodies and anti-HD IgM remain at high levels in chronic HDV infection, and HDV RNA is present.

Autoimmune type 1 (classic) hepatitis is characterized by the presence of titers of 1 : 80 or higher of antinuclear (ANA), anti–smooth muscle (SMA), antiactin, and anti-asialoglycoprotein receptor antibodies. Type 2 autoimmune hepatitis is characterized by similar elevations of anti– liver-kidney microsomal 1antibodies and anti–liver cytosol 1 antibodies (anti-LKM1) without antinuclear or anti–smooth muscle antibodies. Type 3 is characterized by elevation of anti-SLA (auto-antibodies against soluble liver and pancreas antigen) without ANA, SMA and LKM-1. Liver biopsy shows features that are typical of all chronic types of hepatitis, except plasma cell infiltrates.

Hepatic ultrasound can determine the texture and size of the liver and spleen, exclude hepatic masses, and assess the gallbladder, intrahepatic bile ducts, and portal venous flow. Computed tomography and magnetic resonance imaging of the liver are helpful if a mass or other abnormality is found by ultrasound. Hepatic elastography can assess liver stiffness as a marker of fibrosis.

Liver biopsy is usually critical for diagnosis and to determine the severity of disease. Hepatocellular necrosis is typically eosinophilic degeneration or ballooning degeneration throughout the parenchyma, greater in the periportal area, spotty, or piecemeal. Fibrosis also typically begins in the periportal regions and can link adjacent portal areas or portal and central areas (bridging fibrosis), distort the hepatic architecture, and lead to cirrhosis and portal hypertension. The histologic grade of chronic hepatitis can be determined by combining scores for periportal necrosis and inflammation, lobular necrosis and inflammation, and portal inflammation.

Markers of viral hepatits:

	Antigen(s)	Antibodies	Remarks
HCV	C100-3 C33c C22-3 NS5	Anti-HCV	Bloodborne agent, formerly labeled non-A, non-B hepatitis Acute diagnosis: anti-HCV (C33c, C22-3, NS5), HCV RNA Chronic diagnosis: anti-HCV (C100-3, C33c, C223, NS5) and HCV RNA;

			cytoplasmic location in hepatocytes
HBV	HBsAg HBcAg HBeAg HBcAg HBeAg HBsAg	Anti-HBs Anti-HBc Anti-HBe Anti-HBc Anti-HBe Anti-HBs	Bloodborne virus; carrier state Acute diagnosis: HBsAg, IgM anti-HBc Chronic diagnosis: IgG anti-HBc, HBsAg Markers of replication: HBeAg, HBV DNA Liver, lymphocytes, other organs Nucleocapsid contains DNA and DNA polymerase; present in hepatocyte nucleus; HBcAg does not circulate; HBeAg (soluble, nonparticulate) and HBV DNA circulate—correlate with infectivity and complete virions HBsAg detectable in >95% of patients with acute hepatitis B; found in serum, body fluids, hepatocyte cytoplasm; anti-HBs appears following infection—protective antibody
HDV	HBsAg HDAg	Anti-HBs Anti-HDV	Defective RNA virus, requires helper function of HBV (hepadnaviruses); HDV antigen (HDAg) present in hepatocyte nucleus Diagnosis: anti-HDV, HDV RNA; HBV/HDV co-infection—IgM anti-HBc and anti-HDV; HDV superinfection—IgG anti-HBc and anti-

			HDV

Evaluation of a patient with a suspected drug reaction is directed toward establishing the timeline for all drugs or herbs the patient may have taken. Responsible drugs have usually been started between 5 and 90 days before the onset of symptoms. Evidence of viral hepatitis, gallstones, alcoholic liver disease, pregnancy, severe right heart failure, or a period of hypotension points to these specific causes. Less commonly, cytomegalovirus, Epstein-Barr virus, or herpesviruses can cause hepatic injury, primarily in immunosuppressed individuals. If all these causes can be excluded, the temporal relationship fits, and the patient begins to improve after withdrawal of the drug, the diagnosis is more secure. Liver biopsy is of limited value because the histologic picture in most cases of drug-induced liver injury is no different from that of viral hepatitis. Nevertheless, an occasional liver biopsy specimen in an enigmatic case might reveal eosinophils or granulomas, consistent with a drug reaction.

Critical to the diagnosis of NAFLD is a careful history to be sure that alcohol ingestion is less than 20 g/day. Routine laboratory testing for other common liver diseases (e.g., hepatitis B and C, hemochromatosis), as well as less common ones (e.g., Wilson disease, α1-antitrypsin deficiency, autoimmune liver diseases), should be performed. Imaging studies can confirm characteristic features of a fatty liver (e.g., bright liver on ultrasound). These findings are nonspecific, however, and the ultimate diagnosis of NAFLD or NASH requires liver biopsy. The principal treatments are dietary changes and weight loss, but some medications can also be helpful in selected patients.

Patients with alcoholic liver disease may have signs and symptoms from underlying alcoholism as well as those caused by liver disease. Stigmata of chronic alcoholism include palmar erythema, spider nevi, bilateral gynecomastia, testicular atrophy, bilateral parotid enlargement, and Dupuytren's contractures. The clinical features of liver disease will depend on the stage of alcoholic liver disease, that is, whether a patient has alcoholic fatty liver or more advanced liver disease such as alcoholic hepatitis and cirrhosis. Patients with alcoholic fatty liver disease are generally asymptomatic, but some patients may have anorexia, fatigue, right upper quadrant discomfort, and tender hepatomegaly. These patients may also have biochemical evidence of alcoholism and alcoholic liver disease with macrocytosis as well as elevated levels of aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (GGT). Patients with alcoholic fatty liver typically do not have jaundice, ascites, or splenomegaly. Patients with alcoholic hepatitis may have a more dramatic presentation with severe malaise, fatigue, anorexia, fever, evidence of protein-calorie malnutrition, and features of decompensated liver disease, including jaundice, coagulopathy, ascites, and encephalopathy. Physical examination invariably shows at least some features of chronic alcoholism, and jaundice, ascites, and splenomegaly are common. The laboratory examination is typically abnormal. Common hematologic abnormalities include leukocytosis with neutrophil predominance, macrocytic anemia, thrombocytopenia, and a prolonged prothrombin time. Liver biochemistries are abnormal with an elevated AST and ratio of AST to alanine transferase (ALT), alkaline phosphatase, GGT, and total bilirubin, but decreased levels of serum albumin. The AST rarely exceeds 300 IU/L. Serum electrolyte abnormalities including hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia are frequent. The diagnosis of alcoholic liver disease strongly depends on the history of excessive alcohol consumption and the presence of liver disease. Although laboratory abnormalities are not specific for alcoholic liver disease, they can be quite suggestive in the context of excessive alcohol consumption. An AST/ALT ratio of more than 2 is typical in alcoholic liver disease, and ALT values greater than 150 to 200 IU/L are very rare in alcoholic

liver disease. Serology testing for co-existing chronic viral hepatitis is critical. Diagnostic dilemmas arise when a patient denies excessive alcohol consumption in the face of clinical features that are suggestive of alcoholic liver disease. Interviewing family members regarding specific alcohol consumption may be helpful in the accurate ascertainment of alcohol consumption. Elevated blood levels of carbohydrate-deficient transferrin, which is a form of transferrin with fewer than the four sialic acid chains present in normal transferrin, can identify recent heavy alcohol consumption. Hepatic imaging by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) will show changes consistent with hepatic steatosis or more advanced forms of liver disease, such as alcoholic hepatitis and cirrhosis. Imaging is also important to exclude other forms of liver disease, including malignancy and biliary obstruction. Imaging findings specific for alcoholic liver disease include an enlarged caudate lobe, greater visualization of the right posterior hepatic notch, and focal fat sparing or geographic fat distribution. Because specific treatment for alcoholic hepatitis may be harmful in patients with other liver diseases, it is very important to exclude other predominant or coexisting liver diseases, including chronic viral hepatitis and drug-induced liver injury, especially from acetaminophen, by history, blood tests, and biopsy if needed. Hyperferritinemia generally reflects an acute phase reactant, rather than an iron overload disorder, so it usually will return to normal when the acute liver injury resolves. Liver biopsy is the key to precisely characterizing the nature of alcoholic liver disease and determining whether a patient has fatty liver or more advanced alcoholic hepatitis. Histologic features of alcoholic fatty liver include macrovesicular steatosis that is predominantly zone 3 in nature. In alcoholic hepatitis, the biopsy is more striking and reveals macrovesicular steatosis, lobular neutrophilic infiltration, Mallory's hyaline, balloon degeneration of the hepatocytes, and perivenular fibrosis. In general, patients with alcoholic hepatitis also have histologic evidence of chronic liver injury in the form of more advanced fibrosis (periportal or bridging fibrosis, or cirrhosis).

NAFLD is often asymptomatic but may rarely also cause fatigue and right upper quadrant pain. Physical examination may reveal hepatomegaly, palmar erythema, and spider nevi. If liver disease is advanced, the features of liver failure, such as ascites, encephalopathy, and abdominal collateral vessels, are present. Simple steatosis is benign with a minimal risk of cirrhosis, whereas NASH is progressive and can lead to cirrhosis and liver failure. In up to 20% of patients with NASH, liver histology will worsen and cirrhosis will develop over a 10- to 15-year period. Disease progression during the early phase can be identified only with a repeat liver biopsy, but in later stages, the signs and symptoms of portal hypertension (e.g., abdominal collateral vessels and low platelet count) indicate the development of cirrhosis.

NAFLD is generally suspected when aminotransferase levels are asymptomatically elevated in an individual with metabolic risk factors (obesity and diabetes) or when liver imaging (ultrasound, CT, or MRI) obtained for another reason shows fatty infiltration. The diagnosis of NAFLD requires that there is no history of previous or ongoing significant alcohol consumption, no exposure to steatogenic medications, and no evidence of other causes of liver disease, such as viral hepatitis B or C. Elevated levels of aminotransferases, although common, are not required for the diagnosis of NAFLD. In contrast to alcoholic liver disease, ALT levels are higher than AST levels, but they rarely exceed 250 IU/L. In general, AST and ALT levels do not have diagnostic or prognostic significance.

Mild hyperferritinemia is common and should not be confused with hereditary hemochromatosis. Similarly, low-grade autoantibody (antinuclear antibody, anti–smooth muscle antibody) positivity is not uncommon and should not be confused with autoimmune liver

disease. Because steatosis is common in patients with Wilson's disease, serum ceruloplasmin should be obtained as part of the diagnostic evaluation. Fatty liver on ultrasonogram has a positive predictive value of only 77% and a negative predictive value of only 67% when compared with liver biopsy. Abdominal MRI is more accurate, but its high cost limits its usefulness in routine practice. Because none of these three tests can differentiate simple steatosis from NASH nor identify cirrhosis until hepatic fibrosis has caused overt portal hypertension, liver biopsy is required to establish the presence of NASH or cirrhosis. Common indications for a percutaneous liver biopsyin patients with NAFLD include persistently high aminotransferase levels, inability to exclude a competing or a coexisting cause (e.g., iron overload or autoimmune liver disease), or clinical suspicion of severe liver disease. In patients with NASH, liver histology shows steatosis, inflammation, ballooning, and fibrosis.

Differential diagnosis. Patients with suspected chronic viralor autoimmune hepatitis should be evaluated carefully for fatty liver, alcohol- or drug-induced liver disease, and metabolic liver diseases, each of which can coexist with hepatitis. Liver biopsy can exclude other diagnoses that mimic chronic hepatitis, including fatty liver, alcoholic liver disease, steatohepatitis, drug-induced liver disease, sclerosing cholangitis, iron overload, and veno-occlusive disease.

Liver test patterns in hepatobiliary disorders.

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU, ALT > AST	Normal to <3× normal elevation	Normal	Usually normal. If >5× above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be	AST:ALT >2 suggests alcoholic hepatitis or	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to

	elevated Bilirubinuria	cirrhosis			correct with parenteral vitamin K
Intra- and extrahepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation	Elevated, often >4× normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
(Obstructive jaundice) Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Bilirubinuria Usually normal	Rarely >500 IU Normal to slight elevation	Elevated, often >4× normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase	Normal	Normal

Differences in diagnostic and therapy of viral 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: lamivudine, adefovir, telbivudine
Chronic hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1a	PEG IFN-α plus ribavirin Telaprevirb Boceprevirb
Chronic hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3	IFN-α, PEG IFN-αc
Autoimmune hepatitis	ANAd (homogeneous), anti-LKM1 (±) Hyperglobulinemia	ANA, anti-LKM1 anti-SLAe	Prednisone, azathioprine
Drugassociated —	-	Uncommon	Withdraw drug
Cryptogenic	All negative	None	Prednisone (?), azathioprine (?)

Treatment. Chronic HBV infection is not curable, but it can usually be controlled by appropriate antiviral drugs. HCV infection is curable, but less than 50% of patients who have access to therapy are cured (look table above).

Autoimmune hepatitis responds to immunosuppression with corticosteroids and azathioprine. The clinical symptoms and liver test abnormalities of autoimmune hepatitis generally respond promptly to prednisone, usually at a dose of 20 to 30 mg/ day, with a decrease in serum aminotransferase levels to the normal or nearnormal range within 1 to 3 months; higher doses may be required in patients with more severe disease. Lack of a biochemical or clinical response should lead to reevaluation of the diagnosis. Azathioprine 50 to 100 mg can be combinedwith prednisone or added later to reduce long-term steroid side effects.

Prompt discontinuation of a suspected drug in toxic hepatitis is mandatory. Available antidotes should be used for acetaminophen (N-acetylcysteine) and Amanita poisoning (penicillin 300,000 to 1 million U/kg/day intravenously and thioctic acid 5 to 100 mg every 6 hours intravenously have been recommended, but there are no controlled trials). General supportive therapy ranges from intravenous fluid replacement to intensive monitoring and treatment of patients with hepatic encephalopathy secondary to acute liver failure. Liver transplantation is performed in more than 50% of patients with idiosyncratic drug-induced acute liver failure because the survival rate in this setting without transplantation is less than 20%.

Total abstinence, which is the most important treatment measure, is mandatory for the improvement of the clinical and histologic features of alcoholic liver disease. Its benefits are unequivocal, even in patients with severe decompensation. However, long-term abstinence is difficult to achieve, so a multidisciplinary approach with counseling and medications that promote abstinence should be considered. Disulfiram is not commonly used owing to its poortolerability and hepatotoxicity. Opioid antagonists, such as naltrexone (50 mg/day for up to 6 months or even longer), nalmefene (20 mg/day as maintenance), and acamprosate (333 mg tablets, 2 tablets three times each day for 1 year) can help promote abstinence when used as part of a multidisciplinary approach. If a patient's liver biopsy is consistent with alcoholic hepatitis and there is no evidence ofother inflammatory liver diseases, such as hepatitisC, corticosteroids and pentoxifylline (400 mg three times daily for 28 days) are of some benefit. Prednisolone (40 mg per day for 4 weeks) should be given to carefully selected patients who have a score of greater than 32 on Maddrey's discriminant function (4.6 × [patient's prothrombin time—control prothrombin time] + total bilirubin level) and encephalopathy, but do not have gastrointestinal bleeding or systemic infection. All patients with alcoholic hepatitis and alcoholic cirrhosis should be assessed and treated for protein-calorie malnutrition and micronutrient deficiency.

Lifestyle modification with dietary restriction and regular exercise is the first choice of treatment for NAFLD. It is generally recommended that patients with NAFLD lose 10% of their body weight in a gradual fashion, but this goal is difficult to achieve. If resourcesare available, a multidisciplinary approach with behavioral therapy, dietary advice, and monitoring by a professional nutritionist and an exercise expert is more successful than a prescriptive approach. Statins (e.g., atorvastatin 20 mg daily) with or without vitamins C and E can improve liver test results and reduce subsequent NAFLD. In a large trial, 800 IU of vitamin E administered daily for 2 years significantly improved liver histology. Thiazolidinedione insulin sensitizers (pioglitazone and rosiglitazone) improve steatosis, inflammation, and ballooning, but may not improve fibrosis. Unfortunately, the weight gain that is common with thiazolidinediones may

offset the histologic benefits that they offer. In morbidly obese individuals with NASH and other significant metabolic comorbidities, foregut bariatric surgery can lead to significant improvement in hepatic histology, but the physician must exclude the presence of portal hypertension before offering this type of surgery. Patients with NAFLD often have dyslipidemia that puts them at excessive risk for coronary artery disease; their dyslipidemia should be treated aggressively with statins and other lipidlowering agents, which can be safely administered to patients with NAFLD and NASH. Carefully selected patients with decompensated cirrhosis owing to   NASH can be treated with liver transplantation, but recurrence during the post-transplantation period is common.

LIVER CIRRHOSIS

Definition. Liver cirrhosis is a diffuse process characterized by fibrosis and conversion of normal architecture to structurally abnormal nodules. These ―regenerative‖ nodules lack normal lobular organization and are surrounded by fibrous tissue. The process involves the whole liver and is essentially irreversible.

Classification. Liver cirrhosis can be classified according to etiology (see etiological factors below).

Although cirrhosis is histologically an ―all or nothing‖ diagnosis, clinically it can be classified by its status as compensated or decompensated. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy, or jaundice, which are complications that result from the main consequences of cirrhosis: portal hypertension and liver insufficiency.

When all the causes have been investigated and excluded, cirrhosis is considered ―cryptogenic‖.

According to morphological features: micronodular (nodules 1-3 mm), macronodular (nodules >3mm), mixed, septal.

There are two most commonly used scoring systems in cirrhosis: Child-Pugh (range, 5-15) and model of end-stage liver disease (MELD) score (range, 6-40).

MELD score: $[0.957 \times LN \text{ (creatinine in mg/dL)} + 0.378 \times LN \text{ (bilirubin in mg/dL)} + 1.12 \times LN \text{ (INR)} + 0.643] \times 10$. Where LN is natural logarithm.

Child-Pugh classification: Child A - score of 5-6; Child B - score of 7-9; Child C - score of 10-15 (table 1).

TABLE 1.

Parameters	Points Ascribed		
	1	**2**	**3**
Ascites	None	Grade 1-2 (or easy to treat)	Grade 3-4 (or refractory)
Hepatic encephalopathy	None	Grade 1-2 (or induced by a precipitant)	Grade 3-4 (or spontaneous)
Bilirubin (mg/dL) (μmol/L)	<2 <34	2-3 34–51	>3 >51
Albumin (g/dL) (g/L)	>3.5 >35	2.8-3.5 30–35	<2.8 <30
Prothrombin time (seconds> control) or INR (international normalized ratio)	<4 <1.7	4-6 1.7-2.3	>6 >2.3

Epidemiology. Because many patients with cirrhosis are asymptomatic until decompensation occurs, it is very difficult to assess the real prevalence and incidence of cirrhosis in the general population. The prevalence of chronic liver disease or cirrhosis worldwide is estimated to be 100 (range, 25 to 400) per 100,000 subjects, but it varies widely by country and by region. According to the World Health Organization, about 800,000 people die of cirrhosis annually. Because chronic liver disease affects people in their most productive years of life, it has a significant impact on the economy as a result of premature death, illness, and disability.

Etiological factors. Any chronic liver disease can lead to cirrhosis. Chronic viral hepatitis C and alcoholic liver disease are the most common causes of cirrhosis, followed by nonalcoholic fatty liver disease and chronic hepatitis B.

However, the many other causes of cirrhosis include cholestatic and autoimmune liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and metabolic diseases such as hemochromatosis, Wilson's disease, and α1-antitrypsin deficiency.

It is important to mention that although the entity termed primary biliary cirrhosis assumes the presence of cirrhosis, this term is actually misleading. Primary biliary cirrhosis is an immune-mediated cholestatic chronic liver disease that is characterized by progressive destruction of intrahepatic bile ducts and progresses over time from an initial stage in which fibrosis is minimal (stage 1) to a final stage in which there is well-established cirrhosis (stage 4).

Toxines (including such medicines as amiodarone, methotrexat), hepatic venous outflow obstruction (Budd-Chiari syndrome, veno-occlusive disease, right-sided heart failure) also are the common causes of liver cirrhosis.

Pathogenesis. The key pathogenic feature underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells. Hepatic stellate cells, which are known as Ito cells or perisinusoidal cells, are located in the space of Disse between hepatocytes and sinusoidal endothelial cells. Normally, hepatic stellate cells are quiescent and serve as the main storage site for retinoids (vitamin A). In response to injury, hepatic stellate cells become activated, as a result of which they lose their vitamin A deposits, proliferate, develop a prominent rough endoplasmic reticulum, and secrete extracellular matrix (collagen types I and III, sulfated proteoglycans, and glycoproteins). Additionally, they become contractile hepatic myofibroblasts. Unlike other capillaries, normal hepatic sinusoids lack a basement membrane. The sinusoidal endothelial cells themselves contain large fenestrae (100 to 200 nm in diameter) that allow the passage of large molecules with molecular weights up to 250,000. Collagen deposition in the space of Disse, as occurs in cirrhosis, leads to defenestration of the sinusoidal endothelial cells (―capillarization‖ of the sinusoids), thereby altering exchange between plasma and hepatocytes and resulting in a decreased sinusoidal diameter that is further exacerbated by the contraction of stellate cells.

The two main consequences of cirrhosis are portal hypertension, with the accompanying hyperdynamic circulatory state, and liver insufficiency.

The development of varices and ascites is a direct consequence of portal hypertension and the hyperdynamic circulatory state, whereas jaundice occurs as a result of an inability of the liver to excrete bilirubin (i.e., liver insufficiency).

Encephalopathy is the result of both portal hypertension and liver insufficiency.

Ascites, in turn, can become complicated by infection, which is called spontaneous bacterial peritonitis, and by functional renal failure, which is called hepatorenal syndrome.

Portal Hypertension and the Hyperdynamic Circulatory State. In cirrhosis, portal hypertension results from both an increase in resistance to portal flow and an increase in portal venous inflow. The initial mechanism is increased sinusoidal vascular resistance secondary to deposition of fibrous tissue and subsequent compression by regenerative nodules (fixed

component) and active vasoconstriction (functional component), which is amenable to the action of vasodilators such as nitroprusside and is caused by a deficiency in intrahepatic nitric oxide (NO), as well as enhanced activity of vasoconstrictors. Early in the portal hypertensive process, the spleen grows and sequesters platelets and other formed blood cells, thereby leading to hypersplenism. In addition, vessels that normally drain into the portal system, such as the coronary vein, reverse their flow and shunt blood away from the portal system to the systemic circulation. These portosystemic collaterals are insufficient to decompress the portal venous system and offer additional resistance to portal flow.

As collaterals develop, an increase in portal blood inflow maintains the portal hypertensive state as a result of splanchnic vasodilation, which in turn is secondary to increased production of NO. Thus, the paradox in portal hypertension is that a deficiency of NO in the intrahepatic vasculature leads to vasoconstriction and increased resistance, whereas overproduction of NO in the extrahepatic circulation leads to vasodilation and increased flow.

Varices and Variceal Hemorrhage. The complication of cirrhosis that results most directly from portal hypertension is the development of portal-systemic collaterals, the most relevant of which are those that form through dilation of the coronary and gastric veins and constitute gastroesophageal varices. The initial formation of esophageal collaterals depends on a threshold portal pressure, clinically established by a hepatic venous pressure gradient of 10 to 12 mm Hg, below which varices do not develop. Development of a hyperdynamic circulatory state leads to further dilation and growth of varices and eventually to their rupture and variceal hemorrhage, one of the most dreaded complications of portal hypertension.

Ascites and Hepatorenal Syndrome. Ascites in cirrhosis is secondary to sinusoidal hypertension and retention of sodium. Cirrhosis leads to sinusoidal hypertension by blocking hepatic venous outflow both anatomically by fibrosis and regenerative nodules and functionally by increased postsinusoidal vascular tone. Similar to the formation of esophageal varices, a threshold hepatic venous pressure gradient of 12 mm Hg is needed for the formation of ascites. In addition, retention of sodium replenishes the intravascular volume and allows the continuous formation of ascites.

With progression of cirrhosis and portal hypertension, vasodilation is more pronounced, thereby leading to further activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and resulting in further sodium retention (refractory ascites), water retention (hyponatremia), and renal vasoconstriction (hepatorenal syndrome).

Spontaneous Bacterial Peritonitis. Spontaneous bacterial peritonitis, an infection of ascitic fluid, occurs in the absence of perforation of a hollow viscus or an intra-abdominal inflammatory focus such as an abscess, acute pancreatitis, or cholecystitis. Bacterial translocation, or the migration of bacteria from the intestinal lumen to mesenteric lymph nodes and other extraintestinal sites, is the main mechanism implicated in spontaneous bacterial peritonitis. Impaired local and systemic immune defenses are a major element in promoting bacterial translocation and, together with shunting of blood away from the hepatic Kupffer cells through portosystemic collaterals, allow a transient bacteremia to become more prolonged, thereby colonizing ascitic fluid. Spontaneous bacterial peritonitis occurs in patients with reduced ascites defense mechanisms, such as a low complement level in ascitic fluid. Another factor that promotes bacterial translocation in cirrhosis is bacterial overgrowth attributed to a decrease in small bowel motility and intestinal transit time.

Jaundice. Jaundice in cirrhosis is a reflection of the inability of the liver to excrete bilirubin and is therefore the result of liver insufficiency. However, in cholestatic diseases leading to cirrhosis (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, vanishing bile duct syndrome), jaundice is more likely due to biliary damage than liver insufficiency. Other

indicators of liver insufficiency, such as the prothrombin time or the presence of encephalopathy, help determine the most likely contributor to hyperbilirubinemia.

Encephalopathy. Ammonia, a toxin normally removed by the liver, plays a key role in the pathogenesis of hepatic encephalopathy. In cirrhosis, ammonia accumulates in the systemic circulation because of shunting of blood through portosystemic collaterals and decreased liver metabolism (i.e., liver insufficiency).

The presence of large amounts of ammonia in the brain damages supporting brain cells or astrocytes and leads to structural changes characteristic of hepatic encephalopathy (Alzheimer's type II astrocytosis). Ammonia results in upregulation of astrocytic peripheral-type benzodiazepine receptors, the most potent stimulants of neurosteroid production. Neurosteroids are the major modulators of γ-aminobutyric acid, which results in cortical depression and hepatic encephalopathy. Other toxins, such as manganese, also accumulate in the brain, particularly the globus pallidus, where they lead to impaired motor function. Other yet-to-be-elucidated toxins may also be involved in the pathogenesis of encephalopathy. There are three types of encephalopathy depending on the underlying cause: Type A (acute) – associated with acute liver failure; Type B (bypass) – associated with porto-systemic shunting, the waste is not metabolized because the blood bypasses the liver; Type C (cirrhosis) – associated with cirrhosis and chronic deterioration of liver function. This type is subdivided in episodic, persistent, and minimal. West-Haven criteria are used to estimate the stage of encephalopathy. Latent encephalopathy can be detected by number connection test and line tracing test.

West Haven Criteria for Semi-quantitative Grading of Mental Status	
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Cardiopulmonary Complications. The hyperdynamic circulatory state eventually results in high-output heart failure with decreased peripheral utilization of oxygen, a complication that has been referred to as cirrhotic cardiomyopathy. Vasodilation at the level of the pulmonary circulation leads to arterial hypoxemia, the hallmark of hepatopulmonary syndrome. Normal pulmonary capillaries are 8 µm in diameter, and red blood cells (slightly less than 8 µm) pass through them one cell at a time, thereby facilitating oxygenation. In hepatopulmonary syndrome, the pulmonary capillaries are dilated up to 500 µm, so passage of red cells through the pulmonary capillaries may be many cells thick. As a result, a large number of red cells are not oxygenated, which causes the equivalent of a right-to-left shunt. Conversely, portopulmonary hypertension occurs when the pulmonary bed is exposed to vasoconstrictive substances that may be produced in the splanchnic circulation and bypass metabolism by the liver; the initial result is reversible pulmonary hypertension. However, because these factors result in endothelial

proliferation, vasoconstriction, in situ thrombosis, and obliteration of vessels, irreversible pulmonary hypertension ensues.

Clinical features. The clinical manifestations of cirrhosis range widely, depending on the stage of cirrhosis, from an asymptomatic patient with no signs of chronic liver disease to a patient who is confused and jaundiced and has severe muscle wasting and ascites. The natural history of cirrhosis is characterized by an initial phase, termed compensated cirrhosis, followed by a rapidly progressive phase marked by the development of complications of portal hypertension or liver dysfunction (or both), termed decompensated cirrhosis.

In the compensated phase, portal pressure may be normal or below the threshold level identified for the development of varices or ascites. Nonspecific fatigue, decreased libido, or sleep disturbances may be the only complaints. In this stage, cirrhosis is mostly asymptomatic and is diagnosed either during the evaluation of chronic liver disease or fortuitously during routine physical examination, biochemical testing, imaging for other reasons, endoscopy showing gastroesophageal varices, or abdominal surgery in which a nodular liver is detected. Nonbleeding gastroesophageal varices are asymptomatic, and their presence (without bleeding) does not denote decompensation.

As the disease progresses, portal pressure increases and liver function decreases, thereby resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy, and jaundice. The development of any of these complications marks the transition from a compensated to a decompensated phase. At this stage, there are signs of decompensation: ascites, variceal hemorrhage, jaundice, hepatic encephalopathy, or any combination of these findings. Bleeding from gastroesophageal varices can be manifested as overt hematemesis or melena, or both. The most frequent symptoms associated with ascites are increased abdominal girth, which is often described by the patient as tightness of the belt or garments around the waist, and recent weight gain. When present in small to moderate amounts, ascites can be identified on examination by bulging flanks, flank dullness, and shifting dullness. Patients with hepatorenal syndrome usually have tense ascites that responds poorly to diuretics, but no specific symptoms or signs typify this entity.

The most frequent clinical manifestations of spontaneous bacterial peritonitis are fever, jaundice, and abdominal pain. On physical examination, there is typically abdominal tenderness, with or without rebound tenderness, or ileus (or both).   Hepatic encephalopathy, which is the neuropsychiatric manifestation of cirrhosis, occurs at a rate of approximately 2 to 3% per year. Clinically, it is characterized by alterations in consciousness and behavior ranging from inversion of the sleep-wake pattern and forgetfulness (stage 1); to confusion, bizarre behavior, and disorientation (stage 2); to lethargy and profound disorientation (stage 3); to coma (stage 4). On physical examination, early stages may demonstrate only a distal tremor, but the hallmark of hepatic encephalopathy is the presence of asterixis. Additionally, patients with hepatic encephalopathy may have sweet-smelling breath, a characteristic termed fetor hepaticus.

Hepatopulmonary syndrome is associated with exertional dyspnea, which can lead to extreme debilitation. Clubbing of the fingers, cyanosis, and vascular spiders may be seen on physical examination. Portopulmonary hypertension is manifested as exertional dyspnea, syncope, and chest pain. On examination, an accentuated second sound and right ventricular heave are prominent.

The median time to decompensation, or the time at which half the patients with compensated cirrhosis will become decompensated, is about 6 years.

Progression to death may be accelerated by the development of complications such as recurrent GI bleeding, renal impairment (refractory ascites, hepatorenal syndrome), hepatopulmonary syndrome, and sepsis (spontaneous bacterial peritonitis).

Diagnosis. The diagnosis of cirrhosis should be considered in any patient with chronic liver disease. In asymptomatic patients with compensated cirrhosis, typical signs of cirrhosis may not be present, and the diagnosis may often require histologic confirmation by <u>liver biopsy</u>, which is the ―gold standard‖ for the diagnosis of cirrhosis.

Physical Examination. On physical examination, stigmata of cirrhosis consist of muscle atrophy, mainly involving the bitemporal muscle regions and the thenar and hypothenar eminences; spider angiomas, mostly on the trunk, face, and upper limbs; and palmar erythema involving the thenar and the hypothenar eminences and the tips of the fingers. Although muscular atrophy is a marker of liver insufficiency, spider angiomas and palmar erythema are markers of vasodilation and a hyperdynamic circulation. Males may have hair loss on the chest and abdomen, gynecomastia, and testicular atrophy. Petechiae and ecchymoses may be present as a result of thrombocytopenia or a prolonged prothrombin time. Dupuytren's contracture, which is a thickening of the palmar fascia, occurs mostly in alcoholic cirrhosis.

A pathognomonic feature of cirrhosis is the finding on abdominal examination of a small right liver lobe, with a span of less than 7 cm on percussion, and a palpable left lobe that is nodular with increased consistency. Splenomegaly may also be present and is indicative of portal hypertension. Collateral circulation on the abdominal wall (caput medusae) may also develop as a consequence of portal hypertension.

Absence of any of the aforementioned physical findings does not exclude cirrhosis.

Laboratory Tests. Laboratory test results suggestive of cirrhosis include even subtle abnormalities in serum levels of albumin or bilirubin or elevation of the international normalized ratio.

The most sensitive and specific laboratory finding suggestive of cirrhosis in the setting of chronic liver disease is a low platelet count (<150,000/mm3), which occurs as a result of portal hypertension and hypersplenism.

Other serum markers that are often abnormal include levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), hyaluronic acid, $\alpha_2$macroglobulin, haptoglobin, tissue metalloproteinase inhibitor I, and apolipoprotein A. Decreased synthetic liver function is observed in biochemical analysis and coagulogram according to failed function.

Imaging Studies. Confirmatory imaging tests include computed tomography, ultrasound, and magnetic resonance imaging. Findings consistent with cirrhosis include a nodular contour of the liver, a small liver with or without hypertrophy of the left or caudate lobe, splenomegaly, and in particular, identification of intraabdominal collateral vessels indicative of portal hypertension.

Transient elastography, a new noninvasive technique based on ultrasound wave propagation, measures liver stiffness and appears to be useful in the diagnosis of cirrhosis.

Typical findings on any of these imaging studies, together with a compatible clinical picture, are indicative of the presence of cirrhosis. A liver biopsy then would not be required unless the degree of inflammation or other features require investigation. In decompensated cirrhosis, detection of ascites, variceal bleeding, or encephalopathy in the setting of chronic liver disease essentially establishes the diagnosis of cirrhosis, so a liver biopsy is not necessary to establish the diagnosis.

Portal Pressure Measurements. Direct measurements of portal pressure involve catheterization of the portal vein, are cumbersome, and may be associated with complications. Hepatic vein catheterization with measurement of wedged and free pressure is the simplest, safest, most reproducible, and most widely used method to indirectly measure portal pressure. Portal pressure measurements are expressed as the hepatic venous pressure gradient: the gradient between wedged hepatic venous pressure, which is a measure of sinusoidal pressure, and free

hepatic or inferior vena cava pressure, which is used as an internal zero reference point. In a patient with clinical evidence of portal hypertension (e.g., varices), the hepatic venous pressure gradient is useful in the differential diagnosis of the cause of portal hypertension: it will be normal (3 to 5 mm Hg) in prehepatic causes of portal hypertension, such as portal vein thrombosis, and in intrahepatic but presinusoidal causes, such as schistosomiasis, but will be abnormal (≥6 mm Hg) in sinusoidal causes of portal hypertension, such as cirrhosis, and in postsinusoidal causes, such as veno-occlusive disease. A hepatic venous pressure gradient of 10 mm Hg or greater (—clinically significant‖ portal hypertension) predicts the development of complications of portal hypertension, and its reduction on pharmacologic therapy predicts a favorable outcome in patients with cirrhosis.

Other tests. Upper GI endoscopy remains the main method for diagnosing varices and variceal hemorrhage. Varices are classified as small (straight, minimally elevated veins above the esophageal mucosal surface), medium (tortuous veins occupying less than one third of the esophageal lumen), or large (occupying more than one third of the esophageal lumen).

The initial, most cost-effective, and least invasive method to confirm the presence of ascites is abdominal ultrasonography. Diagnostic paracentesis is a safe procedure that should be performed in every patient with new-onset ascites, even in those with coagulopathy. Ultrasound guidance should be used in patients in whom percussion cannot locate the ascites or in whom a first paracentesis attempt does not yield fluid. The fluid in a patient with new-onset ascites should always be evaluated for albumin (with simultaneous estimation of serum albumin), total protein, polymorphonuclear (PMN) blood cell count, bacteriologic cultures, and cytology. The diagnosis of hepatic encephalopathy is clinical and based on the history and physical examination showing alterations in consciousness and behavior, as well as the presence of asterixis. Ammonia levels are unreliable, and there is poor correlation between the stage of hepatic encephalopathy and ammonia blood levels. Therefore, measurements of ammonia are not useful. Psychometric tests and an electroencephalogram are typically used in research but are not useful for clinical diagnosis.

Complications. Complications of cirrhosis result from portal hypertension or liver insufficiency. Varices and variceal hemorrhage are a direct consequence of portal hypertension. Ascites results from sinusoidal portal hypertension and can be complicated by infection (spontaneous bacterial peritonitis) or renal dysfunction (hepatorenal syndrome). Hepatic encephalopathy results from portosystemic shunting (i.e., portal hypertension) and liver insufficiency. Jaundice results solely from liver insufficiency. The development of hepatocellular carcinoma may accelerate the course of the disease at any stage. Anaemia, thrombocytopenia and coagulopathy are the common complications in such patients.

Differential diagnosis. The main goal in differential diagnosis of cirrhosis is to determine the reason of it. Thus, markers of viral hepatitis should be identified.

Autoimmune and metabolic disorders, influence of alcohol, drugs and other toxins have to be excluded.

The most common cause of ascites is cirrhosis, which accounts for 80% of cases. Peritoneal malignancy (e.g., peritoneal metastases from GI tumors or ovarian cancer), heart failure, and peritoneal tuberculosis together account for another 15% of cases. The serum-ascites albumin gradient and ascites protein levels are useful in the differential diagnosis of ascites. The serum-ascites albumin gradient correlates with sinusoidal pressure and will therefore be elevated (>1.1 g/dL) in patients in whom the source of ascites is the hepatic sinusoid (e.g., cirrhosis or cardiac ascites). Protein levels in ascitic fluid are an indirect marker of the integrity of the hepatic sinusoids: normal sinusoids are permeable structures that —leak‖ protein, whereas sinusoids in cirrhosis are —capillarized‖ and do not leak as much protein. The three main causes

of ascites—cirrhosis, peritoneal malignancy or tuberculosis, and heart failure— can easily be distinguished by combining the results of both the serum-ascites albumin gradient and ascites total protein content. Cirrhotic ascites typically has a high serum-ascites albumin gradient and low protein, cardiac ascites has a high serum-ascites albumin gradient and high protein, and ascites secondary to peritoneal malignancy typically has a low serum-ascites albumin gradient and high protein.

Cardiac etiology should be certainly excluded.

Treatment. Treatment of cirrhosis should ideally be aimed at interrupting or reversing fibrosis. However, antifibrotic drugs have not been shown to reverse fibrosis consistently or improve outcomes in cirrhotic patients. Treatment of compensated cirrhosis is currently directed at preventing the development of decompensation by treating the underlying liver disease (e.g., antiviral therapy for hepatitis C or B) to reduce fibrosis and prevent decompensation; avoiding factors that could worsen liver disease, such as alcohol and hepatotoxic drugs (Nonsteroidal anti-inflammatory drugs, Isoniazid, Valproic acid, Erythromycin, Amoxicillin-clavulanate, Ketoconazole, Chlorpromazine, Ezetimibe etc.); and screening for varices (to prevent variceal hemorrhage) and for hepatocellular carcinoma (to treat at an early stage).

- Prednisone and azathioprine - For autoimmune hepatitis;
- Interferon and other antiviral agents - For hepatitis B and C;
- Phlebotomy - For hemochromatosis;
- Ursodeoxycholic acid - For primary biliary cirrhosis;
- Trientine and zinc - For Wilson disease.

Treatment of decompensated cirrhosis focuses on specific decompensating events and the option of liver transplantation.

- <u>Hepatorenal syndrome</u> - patients with early hepatorenal syndrome may be salvaged by aggressive expansion of intravascular volume with albumin and fresh frozen plasma and by avoidance of diuretics.

Nephrotoxic medications, including aminoglycoside antibiotics, should be avoided in patients with cirrhosis. Patients with early hepatorenal syndrome may be salvaged by aggressive expansion of intravascular volume with albumin and fresh frozen plasma and by avoidance of diuretics. The use of renal-dose dopamine is not effective.

- <u>Hepatic encephalopathy</u> - pharmacologic treatment includes the administration of lactulose and antibiotics.

The main treatment for encephalopathy is lactulose syrup. This nonabsorbable disaccharide stimulates the passage of ammonia from tissues into the gut lumen and inhibits intestinal ammonia production. Initial lactulose dosing is 30 mL orally once or twice daily. Dosing is increased until the patient has 2-4 loose stools per day. Dosing should be reduced if the patient complains of diarrhea, abdominal cramping, or bloating. Higher doses of lactulose may be administered via either a nasogastric or rectal tube to hospitalized patients with severe encephalopathy.

Antibiotics serve as second-line agents. They work by decreasing the colonic concentration of ammoniagenic bacteria. Neomycin dosing is 250-1000 mg orally 2-4 times daily. Treatment with neomycin may be complicated by ototoxicity and nephrotoxicity. Rifaximin (Xifaxan) is a nonabsorbable antibiotic that received FDA approval in 2004 for the treatment of travelers' diarrhea and was given approval in 2010 for the reduction of recurrent hepatic encephalopathy. This drug was also approved in May 2015 for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). Data from Europe suggest that rifaximin can decrease colonic levels of ammoniagenic bacteria, with resulting improvement in the symptoms of hepatic encephalopathy.

- Ascites - treatment can include sodium restriction and the use of diuretics, large-volume paracentesis, and shunts (peritoneovenous, portosystemic, transjugular intrahepatic portosystemic).

Spironolactone (Aldactone) blocks the aldosterone receptor at the distal tubule. It is dosed at 50-300 mg once daily. Although the drug has a relatively short half-life, its blockade of the aldosterone receptor lasts for at least 24 hours. Adverse effects of spironolactone include hyperkalemia, gynecomastia, and lactation. Other potassium-sparing diuretics, including amiloride and triamterene, may be used as alternative agents, especially in patients complaining of gynecomastia.

Furosemide (Lasix) may be used as a solo agent or in combination with spironolactone. The drug blocks sodium reuptake in the loop of Henle. It is dosed at 40-240 mg daily in 1-2 divided doses. Patients infrequently need potassium repletion when furosemide is dosed in combination with spironolactone.

Aggressive diuretic therapy in hospitalized patients with massive ascites can safely induce a weight loss of 0.5-1kg daily, provided that patients undergo careful monitoring of renal function. Diuretic therapy should be held in the event of electrolyte disturbances, azotemia, or induction of hepatic encephalopathy.

Vasopressin V2 receptor antagonists are a class of agents with the potential to increase free-water excretion, improve diuresis, and decrease the need for paracentesis.

- Vitamin K and a blood plasma can be given in emergencies to treat episodes of bleeding.

Nonselective beta-blockers (propranolol, nadolol) reduce portal pressures and are used in the primary and secondary prophylaxis of variceal hemorrhage. β-adrenergic blockers reduce portal pressure by producing splanchnic vasoconstriction and decreasing portal venous inflow. Propranolol is initiated at a dose of 20 mg orally twice a day, whereas nadolol is initiated at a dose of 20 mg orally every day. The dose should be titrated to produce a resting heart rate of about 50 to 55 beats per minute. In patients who have early cirrhosis without moderate-to-large varices, beta-blockers do not prevent the development of varices and also result in adverse effects. The clinical window opens when moderate-to-large esophageal varices develop, with or without variceal bleeding, and beta-blockers are indicated for primary and secondary prophylaxis of variceal bleeding. Increasingly, evidence suggests that the clinical window for beta-blockers closes and that they are no longer effective when refractory ascites, hypotension, the hepatorenal syndrome, spontaneous bacterial peritonitis, sepsis, or severe alcoholic hepatitis develops, owing to unfavorable hemodynamic effects in advanced cirrhosis.

The use of invasive measurement of the hepatic venous pressure gradient to guide beta-blocker use may predict clinical efficacy and provide useful prognostic information.

Although the role of beta-blockers in patients with end-stage cirrhosis remains controversial, there is increasing awareness of the role of blood pressure in the survival of patients with cirrhosis. The most recent Baveno VI consensus guidelines regarding portal hypertension recommend the discontinuation of beta-blockers when the systolic blood pressure is less than 90 mm Hg, the serum sodium concentration is less than 120 mmol per liter, or acute kidney injury has developed. Our practice is to discontinue beta-blockers when the systolic blood pressure is less than 100 mm Hg, because a blood pressure of 100/73 mm Hg is required to obtain the mean arterial pressure of 82 mm Hg that has been described to correlate with survival.

Analgesic agents must be carefully selected in patients with cirrhosis. Because of the risk of acute renal failure and gastrointestinal bleeding, nonsteroidal antiinflammatory drugs are contraindicated, except for low-dose aspirin in patients in whom the severity of cardiovascular disease exceeds the severity of cirrhosis. Opiates should be used cautiously or avoided, because they may precipitate or aggravate hepatic encephalopathy. Tramadol is safe in low doses, and

topical medications such as lidocaine patches are generally safe. Acetaminophen is effective and safe in patients with liver disease, provided that the patient does not drink alcohol.

Patients should be referred for consideration for liver transplantation after the first signs of hepatic decompensation.

Materials for self-control:
Situation tasks:

1.   A 22 years old woman complained of right subcostal pain, nausea, and decreased appetite. She fell ill 2 months after appendectomy when jaundice appeared. She was treated in an infectious hospital. 1 year later mentioned symptoms recurrenced. Examination detected subicteric sclerae, enlarged firm liver. What is the preliminary diagnosis? What additional tests are necessary?

2.   32 years old patient suffers from chronic viral hepatitis. He complains of dull pain in the right subcostal area, nausea, dry feeling in mouth. Objectively: liver size is 13-21-11 cm (according to Kurlov), spleen is enlarged by 2 cm, aspartate aminotransferase is 3,2 micromole/l·h, alanine aminotransferase - 4,8 millimole/l·h. Serological study revealed HBeAg, high concentration of DNA HBV. What is the diagnosis? What additional tests are necessary for the patient? What is the treatment?

3.   A woman, 42 years old, is suffering from micronodular cryptogenic hepatic cirrhosis. During the last week state worsened: cramps and dizzinesses appeared, memory had worsened, icterus increased. What complication developed? What research can explain the reason of worsening?

Tests:

1. A 24-year-old female patient complains of pain in the right hypochondrium that is getting worse after taking meals; nausea, fever up to37,7oC, icteric skin, pain in the large joints. These presentations have been observed for 8 months. Objectively: hepatosplenomegaly. Blood test results: ESR- 47 mm/h, total bilirubin - 86,1 mmol/l, direct bilirubin - 42,3 mmol/l. Total protein - 62 g/l, albumins - 40%, globulins - 60%, gamma globulins - 38%. Viral hepatitis markers were not detected. The antibodies to smooth muscle cells are present. On ultrasound the portal vein diameter was of 1 cm. What is the most likely diagnosis?
   A. Primary biliary cirrhosis
   B. Autoimmune hepatitis
   C. Gilbert's syndrome
   D. Cholangiogenic hepatitis
   E. Hemachromatosis

2. A 40 y. o. patient was admitted to the gasteroenterology department with skin itching, jaundice, discomfort in the right subcostal area, generalized weakness. On examination: skin is jaundice, traces of scratches, liver is +5 cm, spleen is 6x8 cm. In blood: alkaline phosphatase - 2,0 mmol/(hour*L), general bilirubin - 60 mkmol/L, cholesterol - 8,0 mmol/L. What is the leading syndrome in the patient?
   A. Cytolytic

B. Cholestatic

C. Mesenchymal inflammatory

D. Asthenic

E. Liver-cells insufficiency

3. 23 years old patient has complaints on pain in the right subcostal area, periodic bitter belch, nausea, appetite loss. From the anamnesis: appendectomy had been conducted three years ago. In 2 months icterus appeared and patient was treated in infectious hospital. At the examination liver is enlarged on 2 cm. In blood: general bilirubin - 76 mkmol/l, direct bilirubin - 14,9 mkmol/, ALT - 1,35. What disease are you thinking of?

A. Cirrhosis of liver

B. Chronic cholangitis

C. Chronic cholecystitis

D. Benign Gilber`s icterus

E. Chronic hepatitis B

4. Patient K., 24 years old, complains of pain in the right subcostum and joints, icteric skin, weight loss - 10 kg for a year, temperature 38°C. A disease began after childbirth half a year ago. Objectively: icteric skin and scleras, there are xanthomas on eyelids. Liver +4 cm, dense, painful, edge is sharp. Spleen +2 cm. Blood tests: AST - 2,8, ALT - 3,4, general bilirubin - 97,6, free - 54,6, HbsAg was not determined. Name the basic mechanism of pathogenesis:

A. Viral infection

B. Toxic damage of hepatocytes

C. Fatty dystrophy of liver

D. Violation of bile outflow

E. Autoimmune

5. 20 years old patient was diagnosed chronic viral hepatitis in gastroenterologic unit. What group of preparations can be included to the base therapy?

A. Hepatoprotector

B. Antibacterial

C. Anabolic steroid hormones

D. Vitamins

E. Glucocorticoids and cytostatic

6. Patient, 49 years old, complains of general weakness, increased ascites during 2 months. After the abdominal puncture 10l of pale yellow transparent liquid was got. Painless liver is palpated with acute even edge, it comes under a costal arc on 4 cm and spleen is 2 cm below an edge of costal arc. The syndrome of cytolysis is absent. Roentgenologically stomach and duodenum have no changes. What disease is it possible to think about?

A. Pick`s pseudocirrhosis

B. Cryptogenic micronodular hepatic cirrhosis

C. Chronic toxic hepatitis

D. Biliary hepatic cirrhosis

E. Phlebitis of hepatic vein (Budd – Chiari disease)

7. 49 years old man, invalid of the I group, treats concerning the hepatic cirrhosis during a few years. For the last months abdomen increased in size, weakness intensified. He took furosemide daily for 2 weeks. What blood changes of electrolytes do you expect to find out?

A. Hypokaliemia
B. Hypocalciemia
C. Hypernatriemia
D. Hypercalciemia
E. Hyperkaliemia

8. A man, 46 years old, complains of vomiting with bright red blood. In the anamnesis: micronodular hepatic cirrhosis of viral etiology for 5 years. During last half year increasing abdominal size due to ascites was observed. What preparation is it necessary to begin with?

A. Cordiamin - 2 ml intramuscular
B. Intravenous vasopressin - 20 units
C. Mesaton 1% - 2 ml intramuscular
D. Prednizolon - 20 mg intravenous
E. Swallowing of ice pieces

9. Patient I., 50 years old, was got to hospital in extremely hard condition. At the examination: common sense is absent, skin and scleras are icteric. Liver is enlarged, splenomegaly. Ascites is determined, acidic breathing, tachycardia, AP 90/40. There are subdermal hematomas, erythemas of hands. Metabolic hyperacidity: pH - 7,1, AST - 1,8, ALT - 2,1. General bilirubin of blood - 334,2 mkmol/l, sodium of blood serum - 122 mmol/l, potassium of blood serum - 5,9 mmol/l. Worsening of patient's condition is associated with:

A. Thrombosis of mesenterial vessels
B. Poisoning with alcohol substitutes
C. Heart failure, III stage
D. Violation of cerebral blood circulation
E. Hepatic coma

10. A patient, 44 years old, abuses alcohol for a long time. Objectively: thenar and hypothenar are red, vascular stars on the front surface of thorax, veins of anterior abdominal wall are dilated. Abdomen is bloated, free liquid is determined in abdominal cavity. Liver + 4 cm, smooth, unpainful. The edge of spleen is palpated. In blood: L - 8,7x109/l. What complication developed?

A. Subacute hepatic dystrophy
B. Portal hypertension
C. Coagulopathy
D. Thrombosis of mesenteries vessels
E. Hypersplenism

Correct answers forthe situation tasks:

1. Chronic viral hepatitis.Biochemical blood analysis (liver tests), markers of hepatitis in serum, US of abdominal cavity, Fibro-test, Acti-test.

Correct answers for the situation tasks:

1. Chronic viral hepatitis. Biochemical blood analysis (liver tests), markers of hepatitis in serum, US of abdominal cavity, Fibro-test, Acti-test.
2. Chronic viral hepatitis B. US of abdominal cavity, Fibro-test, Acti-test. a-interferon.
3. Hepatic encephalopathy. Determination of ammonia in blood serum.

The answers for the tests:
1-B, 2-B, 3-E, 4-E, 5-A, 6-B, 7-A, 8-B, 9-E, 10-C.

Recommended literature:

1. Goldman's Cecil medicine // [edited by] Lee Goldman, Andrew I. Schafer. – 24th ed. USA 2012, Elsevier p. 2569
2. Harrison's Principles of Internal Medicine // D.Kasper, A.Fauci, S.Hauser, D. Longo -19 ed. – N.Y.: McGraw-Hill Professional, 2015. – Vol. 1, Vol.2. - 3000 p.
3. http://emedicine.medscape.com/article/172356-overview

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