

**MINISTRY OF HEALTHCARE OF UKRAINE  
HSEEU "Ukrainian Medical Stomatological Academy"**

**"Approved"**

at the meeting of internal  
medicine №1 department

Head of Department  
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**Protocol № 4 from 13.10.2016**

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

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in gastroenterology clinic
<i>Study subject</i>	<b>Management of the patients with jaundice</b>
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

Poltava 2016.

**1. Relevance of the topic:** While extrahepatic biliary obstruction and drugs are common causes of new-onset jaundice in developed countries, infections remain the leading cause in developing countries. Liver involvement and jaundice are observed with numerous infections. Cholestasis, inflammation of pancreatic head are the common reasons of icterus. It is important to differentiate GI diseases with diseases of blood.

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

Specific goals:

- To select the information indicating the cause of jaundice;
- To create a scheme of diagnostic search;
- To identify the other signs of diseases that runs with jaundice (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 jaundice;
- 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, biliary tract, 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 gastrointestinal 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, indications and contraindications for the IPP, H <sub>2</sub> -blockers, antacids,	Prescribe the drugs of these groups

	prokinetics, antibiotics, enzymes, pain killers, antispasmodics	
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#### 4. Do the tasks for independent work during preparation for classes.

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

Term	Definition
Chronic cholecystitis	is an inflammation of the gallbladder with the presence of gallbladder-related symptoms because of motor dysfunction and changes in chemical and physical bile content (dyscholia).
Cholelithiasis	is a stone forming within the gallbladder out of bile components.
Functional biliary disorders	symptom complexes not explained by a clearly identified mechanism or by a structural alteration.
Cholekinetics	are substances which increase the contractile power of the bile duct.
Choleretics	are substances that increase the volume of secretion of bile from the liver as well as the amount of solids secreted.
Chronic hepatitis	are liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months.
Syndrome of cytotoxicity	complex of symptoms that includes clinical signs and elevated liver intracellular enzymes (AST, ALT, GGT, LDH) in blood that indicates on necrosis.
Syndrome of cholestasis	complex of symptoms that includes jaundice, skin itching, dark urine, light-colored stool and elevated GGT, alkaline phosphatase, cholesterol, direct and total bilirubin in blood serum.
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 jaundice, name and define diseases which are characterized by it.
2. Specify the risk factors for diseases of liver, gallbladder, pancreas, biliary tract.
3. The pathophysiological mechanisms of jaundice.
4. Diagnostic criteria of cholecystitis, functional disorders of biliary tract, hepatitis, liver cirrhosis.
5. Modern classifications of cholecystitis, functional disorders of biliary tract, hepatitis, liver cirrhosis.
6. Specify the principles and features of cholecystitis, functional disorders of biliary tract, hepatitis, liver cirrhosis pharmacotherapy according to modern recommendations.

7. What lifestyle modifications should be recommended for patients with jaundice according to the reason?

### **Topic Content**

#### **MANAGEMENT OF PATIENTS WITH JAUNDICE**

Jaundice, or icterus, is a yellowish discoloration of tissue resulting from the deposition of bilirubin. Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is a sign of either liver disease or, less often, a hemolytic disorder. The degree of serum bilirubin elevation can be estimated by physical examination. Slight increases in serum bilirubin level are best detected by examining the sclerae, which have a particular affinity for bilirubin due to their high elastin content. The presence of scleral icterus indicates a serum bilirubin level of at least 51  $\mu\text{mol/L}$  (3 mg/dL). The ability to detect scleral icterus is made more difficult if the examining room has fluorescent lighting. If the examiner suspects scleral icterus, a second site to examine is underneath the tongue. As serum bilirubin levels rise, the skin will eventually become yellow in light-skinned patients and even green if the process is long-standing; the green color is produced by oxidation of bilirubin to biliverdin.

The differential diagnosis for yellowing of the skin is limited. In addition to jaundice, it includes carotenoderma, the use of the drug quinacrine, and excessive exposure to phenols. Carotenoderma is the yellow color imparted to the skin of healthy individuals who ingest excessive amounts of vegetables and fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches, and oranges. In jaundice the yellow coloration of the skin is uniformly distributed over the body, whereas in carotenoderma the pigment is concentrated on the palms, soles, forehead, and nasolabial folds. Carotenoderma can be distinguished from jaundice by the sparing of the sclerae. Quinacrine causes a yellow discoloration of the skin in 4–37% of patients treated with it.

Another sensitive indicator of increased serum bilirubin is darkening of the urine, which is due to the renal excretion of conjugated bilirubin. Patients often describe their urine as tea- or cola-colored. Bilirubinuria indicates an elevation of the direct serum bilirubin fraction and, therefore, the presence of liver disease.

Serum bilirubin levels increase when an imbalance exists between bilirubin production and clearance. A logical evaluation of the patient who is jaundiced requires an understanding of bilirubin production and metabolism.

Bilirubin, a tetrapyrrole pigment, is a breakdown product of heme (ferroprotoporphyrin IX). About 70–80% of the 250–300 mg of bilirubin produced each day is derived from the breakdown of hemoglobin in senescent red blood cells. The remainder comes from prematurely destroyed erythroid cells in bone marrow and from the turnover of hemoproteins such as myoglobin and cytochromes found in tissues throughout the body.

The formation of bilirubin occurs in reticuloendothelial cells, primarily in the spleen and liver. The first reaction, catalyzed by the microsomal enzyme heme oxygenase, oxidatively cleaves the  $\alpha$  bridge of the porphyrin group and opens the heme ring. The end products of this reaction are biliverdin, carbon monoxide, and iron. The second reaction, catalyzed by the cytosolic enzyme biliverdin reductase, reduces the central methylene bridge of biliverdin and converts it to bilirubin. Bilirubin formed in the reticuloendothelial cells is virtually insoluble in water due to tight internal hydrogen bonding between the water-soluble moieties of bilirubin—i.e., the bonding of the propionic acid carboxyl groups of one dipyrrolic half of the molecule with the imino and lactam groups of the opposite half. This configuration blocks solvent access to the polar residues of bilirubin and places the hydrophobic residues on the outside. To be transported in blood, bilirubin must be solubilized. Solubilization is accomplished by the reversible, noncovalent binding of bilirubin to albumin. Unconjugated bilirubin bound to albumin is transported to the liver. There, the bilirubin—but not the albumin—is taken up by hepatocytes via a process that at least partly involves carrier-mediated membrane transport. No specific bilirubin transporter has yet been identified.

After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins including proteins in the glutathione-S-transferase superfamily. These proteins serve both to reduce efflux of bilirubin back into the serum and to present the bilirubin for conjugation. In the endoplasmic reticulum, bilirubin is solubilized by conjugation to glucuronic acid, a process that disrupts the internal hydrogen bonds and yields bilirubin monoglucuronide and diglucuronide. The conjugation of glucuronic acid to bilirubin is catalyzed by bilirubin uridine diphosphate-glucuronosyl transferase (UDPGT). The now-hydrophilic bilirubin conjugates diffuse from the endoplasmic reticulum to the canalicular membrane, where bilirubin monoglucuronide and diglucuronide are actively transported into canalicular bile by an energy-dependent mechanism involving the multidrug resistance-associated protein 2 (MRP2).

The conjugated bilirubin excreted into bile drains into the duodenum and passes unchanged through the proximal small bowel. Conjugated bilirubin is not taken up by the intestinal mucosa. When the conjugated bilirubin reaches the distal ileum and colon, it is hydrolyzed to unconjugated bilirubin by bacterial  $\beta$ -glucuronidases. The unconjugated bilirubin is reduced by normal gut bacteria to form a group of colorless tetrapyrroles called urobilinogens. About 80–90% of these products are excreted in feces, either unchanged or oxidized to orange derivatives called urobilins. The remaining 10–20% of the urobilinogens are passively absorbed, enter the portal venous blood, and are re-excreted by the liver. A small fraction (usually <3 mg/dL) escapes hepatic uptake, filters across the renal glomerulus, and is excreted in urine.

**Approach to the patient.** Simply stated, the initial step is to perform appropriate blood tests in order to determine whether the patient has an isolated elevation of serum bilirubin. If so, is the bilirubin elevation due to an increased unconjugated or conjugated fraction? If the hyperbilirubinemia is accompanied by other liver test abnormalities, is the disorder hepatocellular or cholestatic? If cholestatic, is it intra- or extrahepatic? All of these questions can be answered with a thoughtful history, physical examination, and interpretation of laboratory and radiologic tests and procedures.

The bilirubin present in serum represents a balance between input from the production of bilirubin and hepatic/biliary removal of the pigment. Hyperbilirubinemia may result from overproduction of bilirubin; impaired uptake, conjugation, or excretion of bilirubin; or regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts. An increase in unconjugated bilirubin in serum results from overproduction, impaired uptake, or conjugation of bilirubin. An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or backward leakage of the pigment. The initial steps in evaluating the patient with jaundice are to determine whether the hyperbilirubinemia is predominantly conjugated or unconjugated in nature and whether other biochemical liver tests are abnormal. Simply stated, the initial step is to perform appropriate blood tests in order to determine whether the patient has an isolated elevation of serum bilirubin. If so, is the bilirubin elevation due to an increased unconjugated or conjugated fraction? If the hyperbilirubinemia is accompanied by other liver test abnormalities, is the disorder hepatocellular or cholestatic? If cholestatic, is it intra- or extrahepatic? All of these questions can be answered with a thoughtful history, physical examination, and interpretation of laboratory and radiologic tests and procedures. The bilirubin present in serum represents a balance between input from the production of bilirubin and hepatic/biliary removal of the pigment. Hyperbilirubinemia may result from overproduction of bilirubin; impaired uptake, conjugation, or excretion of bilirubin; or regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts. An increase in unconjugated bilirubin in serum results from overproduction, impaired uptake, or conjugation of bilirubin. An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or backward leakage of the pigment. The initial steps in evaluating the patient with jaundice are to determine whether the hyperbilirubinemia is predominantly conjugated or unconjugated in nature and whether other biochemical liver tests are abnormal.

The thoughtful interpretation of limited data permits a rational evaluation of the patient. The following discussion will focus solely on the evaluation of the adult patient with jaundice.

The differential diagnosis of isolated unconjugated hyperbilirubinemia is limited. The critical determination is whether the patient is suffering from a hemolytic process resulting in an overproduction of bilirubin (hemolytic disorders and ineffective erythropoiesis) or from impaired hepatic uptake/conjugation of bilirubin (drug effect or genetic disorders).

Hemolytic disorders that cause excessive heme production may be either inherited or acquired. Inherited disorders include spherocytosis, sickle cell anemia, thalassemia, and deficiency of red cell enzymes such as pyruvate kinase and glucose-6-phosphate dehydrogenase. In these conditions, the serum bilirubin level rarely exceeds 86  $\mu\text{mol/L}$  (5 mg/dL). Higher levels may occur when there is coexistent renal or hepatocellular dysfunction or in acute hemolysis, such as a sickle cell crisis. In evaluating jaundice in patients with chronic hemolysis, it is important to remember the high incidence of pigmented (calcium bilirubinate) gallstones found in these patients, which increases the likelihood of choledocholithiasis as an alternative explanation for hyperbilirubinemia.

Acquired hemolytic disorders include microangiopathic hemolytic anemia (e.g., hemolytic-uremic syndrome), paroxysmal nocturnal hemoglobinuria, spur cell anemia, immune hemolysis, and parasitic infections (e.g., malaria and babesiosis). Ineffective erythropoiesis occurs in cobalamin, folate, and iron deficiencies. Resorption of hematomas and massive blood transfusions both can result in increased hemoglobin release and overproduction of bilirubin.

In the absence of hemolysis, the physician should consider a problem with the hepatic uptake or conjugation of bilirubin. Certain drugs, including rifampin and probenecid, may cause unconjugated hyperbilirubinemia by diminishing hepatic uptake of bilirubin. Impaired bilirubin conjugation occurs in three genetic conditions: Crigler-Najjar syndrome types I and II and Gilbert's syndrome. Crigler-Najjar type I is an exceptionally rare condition found in neonates and characterized by severe jaundice (bilirubin  $>342 \mu\text{mol/L}$  [ $>20 \text{ mg/dL}$ ]) and neurologic impairment due to kernicterus, frequently leading to death in infancy or childhood. These patients have a complete absence of bilirubin UDPGT activity, usually due to mutations in the critical 3' domain of the UDPGT gene; are totally unable to conjugate bilirubin; and hence cannot excrete it.

Crigler-Najjar type II is somewhat more common than type I. Patients live into adulthood with serum bilirubin levels of 103–428  $\mu\text{mol/L}$  (6–25 mg/dL). In these patients, mutations in the bilirubin UDPGT gene cause the reduction—but not the complete eradication—of the enzyme's activity. Bilirubin UDPGT activity can be induced by the administration of phenobarbital, which can reduce serum bilirubin levels in these patients. Despite marked jaundice, these patients usually survive into adulthood, although they may be susceptible to kernicterus under the stress of intercurrent illness or surgery.

Gilbert's syndrome is also marked by the impaired conjugation of bilirubin (to approximately one-third of normal) due to reduced bilirubin UDPGT activity. Patients with Gilbert's syndrome have mild unconjugated hyperbilirubinemia, with serum levels almost always  $<103 \mu\text{mol/L}$  (6 mg/dL). The serum levels may fluctuate, and jaundice is often identified only during periods of fasting. The molecular defect in Gilbert's syndrome is linked to a reduction in transcription of the bilirubin UDPGT gene due to mutations in the promoter and, rarely, in the coding region. Unlike both Crigler-Najjar syndromes, Gilbert's syndrome is very common. The reported incidence is 3–7% of the population, with males predominating over females by a ratio of 2–7:1.

Elevated conjugated hyperbilirubinemia is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome. Patients with either condition present with asymptomatic jaundice. The defect in Dubin-Johnson syndrome is the presence of mutations in the gene for MRP2. These patients have altered excretion of bilirubin into the bile ducts. Rotor syndrome may represent a deficiency of the major hepatic drug uptake transporters OATP1B1 and OATP1B3. Differentiating between these syndromes is possible but is clinically unnecessary due to their benign nature.

A complete medical history is perhaps the single most important part of the evaluation of the patient with unexplained jaundice. Important considerations include the use of or exposure to any chemical or medication, whether physician-prescribed, over-the-counter, complementary, or alternative medicines (e.g., herbal and vitamin preparations) or other drugs such as anabolic steroids. The patient should be carefully questioned about possible parenteral exposures, including transfusions, intravenous and intranasal drug use, tattooing, and sexual activity. Other important points include recent travel history; exposure to people with jaundice; exposure to possibly contaminated foods; occupational exposure to hepatotoxins; alcohol consumption; the duration of jaundice; and the presence of any accompanying signs and symptoms, such as arthralgias, myalgias, rash, anorexia, weight loss, abdominal pain, fever, pruritus, and changes in the urine and stool. While none of the latter manifestations is specific for any one condition, any of them can suggest a particular diagnosis. A history of arthralgias and myalgias predating jaundice suggests hepatitis, either viral or drug-related. Jaundice associated with the sudden onset of severe right-upper-quadrant pain and shaking chills suggests choledocholithiasis and ascending cholangitis.

The general assessment should include evaluation of the patient's nutritional status. Temporal and proximal muscle wasting suggests long-standing disease such as pancreatic cancer or cirrhosis. Stigmata of chronic liver disease, including spider nevi, palmar erythema, gynecomastia, caput medusae, Dupuytren's contractures, parotid gland enlargement, and testicular atrophy, are commonly seen in advanced alcoholic (Laennec's) cirrhosis and occasionally in other types of cirrhosis. An enlarged left supraclavicular node (Virchow's node) or a periumbilical nodule (Sister Mary Joseph's nodule) suggests an abdominal malignancy. Jugular venous distention, a sign of right-sided heart failure, suggests hepatic congestion. Right pleural effusion in the absence of clinically apparent ascites may be seen in advanced cirrhosis.

The abdominal examination should focus on the size and consistency of the liver, on whether the spleen is palpable and hence enlarged, and on whether ascites is present. Patients with cirrhosis may have an enlarged left lobe of the liver, which is felt below the xiphoid, and an enlarged spleen. A grossly enlarged nodular liver or an obvious abdominal mass suggests malignancy. An enlarged tender liver could signify viral or alcoholic hepatitis; an infiltrative process such as amyloidosis; or, less often, an acutely congested liver secondary to right-sided heart failure. Severe right-upper-quadrant tenderness with respiratory arrest on inspiration (Murphy's sign) suggests cholecystitis. Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

A battery of tests are helpful in the initial evaluation of a patient with unexplained jaundice. These include total and direct serum bilirubin measurement with fractionation; determination of serum aminotransferase, alkaline phosphatase, and albumin concentrations; and prothrombin time tests. Enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) are helpful in differentiating between a hepatocellular process and a cholestatic process—a critical step in determining what additional workup is indicated. Patients with a hepatocellular process generally have a rise in the aminotransferases that is disproportionate to that in ALP, whereas patients with a cholestatic process have a rise in ALP that is disproportionate to that of the aminotransferases. The serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two.

In addition to enzyme tests, all jaundiced patients should have additional blood tests—specifically, an albumin level and a prothrombin time—to assess liver function. A low albumin level suggests a chronic process such as cirrhosis or cancer. A normal albumin level is suggestive of a more acute process such as viral hepatitis or choledocholithiasis. An elevated prothrombin time indicates either vitamin K deficiency due to prolonged jaundice and malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to correct with parenteral administration of vitamin K indicates severe hepatocellular injury.

The results of the bilirubin, enzyme, albumin, and prothrombin time tests will usually indicate whether a jaundiced patient has a hepatocellular or a cholestatic disease and offer some indication of the duration and severity of the disease. The causes and evaluations of hepatocellular and cholestatic diseases are quite different.

Hepatocellular diseases that can cause jaundice include viral hepatitis, drug or environmental toxicity, alcohol, and end-stage cirrhosis from any cause. Wilson's disease occurs primarily in young adults. Autoimmune hepatitis is typically seen in young to middle-aged women but may affect men and women of any age. Alcoholic hepatitis can be differentiated from viral and toxin-related hepatitis by the pattern of the aminotransferases: patients with alcoholic hepatitis typically have an AST-to-ALT ratio of at least 2:1, and the AST level rarely exceeds 300 U/L. Patients with acute viral hepatitis and toxin-related injury severe enough to produce jaundice typically have aminotransferase levels >500 U/L, with the ALT greater than or equal to the AST. While ALT and AST values <8 times normal may be seen in either hepatocellular or cholestatic liver disease, values 25 times normal or higher are seen primarily in acute hepatocellular diseases. Patients with jaundice from cirrhosis can have normal or only slightly elevated aminotransferase levels.

When the clinician determines that a patient has a hepatocellular disease, appropriate testing for acute viral hepatitis includes a hepatitis A IgM antibody assay, a hepatitis B surface antigen and core IgM antibody assay, a hepatitis C viral RNA test, and, depending on the circumstances, a hepatitis E IgM antibody assay. Because it can take many weeks for hepatitis C antibody to become detectable, its assay is an unreliable test if acute hepatitis C is suspected. Studies for hepatitis D and E viruses, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) may also be indicated. Ceruloplasmin is the initial screening test for Wilson's disease. Testing for autoimmune hepatitis usually includes an antinuclear antibody assay and measurement of specific immunoglobulins.

Drug-induced hepatocellular injury can be classified as either predictable or unpredictable. Predictable drug reactions are dose-dependent and affect all patients who ingest a toxic dose of the drug in question. The classic example is acetaminophen hepatotoxicity. Unpredictable or idiosyncratic drug reactions are not dose-dependent and occur in a minority of patients. A great number of drugs can cause idiosyncratic hepatic injury. Environmental toxins are also an important cause of hepatocellular injury. Examples include industrial chemicals such as vinyl chloride, herbal preparations containing pyrrolizidine alkaloids (Jamaica bush tea) or Kava Kava, and the mushrooms *Amanita phalloides* and *A. verna*, which contain highly hepatotoxic amatoxins.

When the pattern of the liver tests suggests a cholestatic disorder, the next step is to determine whether it is intra- or extrahepatic cholestasis. Distinguishing intrahepatic from extrahepatic cholestasis may be difficult. History, physical examination, and laboratory tests often are not helpful. The next appropriate test is an ultrasound. The ultrasound is inexpensive, does not expose the patient to ionizing radiation, and can detect dilation of the intra- and extrahepatic biliary tree with a high degree of sensitivity and specificity. The absence of biliary dilation suggests intrahepatic cholestasis, while its presence indicates extrahepatic cholestasis. False-negative results occur in patients with partial obstruction of the common bile duct or in patients with cirrhosis or primary sclerosing cholangitis (PSC), in which scarring prevents the intrahepatic ducts from dilating.

Although ultrasonography may indicate extrahepatic cholestasis, it rarely identifies the site or cause of obstruction. The distal common bile duct is a particularly difficult area to visualize by ultrasound because of overlying bowel gas. Appropriate next tests include CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). CT scanning and MRCP are better than ultrasonography for assessing the head of the pancreas and for identifying choledocholithiasis in the distal common bile duct, particularly when the ducts are not dilated. ERCP is the "gold standard" for identifying choledocholithiasis. Beyond its diagnostic capabilities, ERCP allows therapeutic interventions, including the removal of common bile duct



stones and the placement of stents. MRCP has replaced ERCP as the initial diagnostic test in cases where the need for intervention is thought to be small. EUS displays sensitivity and specificity comparable to that of MRCP in the detection of bile duct obstruction. EUS also allows biopsy of suspected malignant lesions, but is invasive and requires sedation.

In patients with apparent intrahepatic cholestasis, the diagnosis is often made by serologic testing in combination with percutaneous liver biopsy. The list of possible causes of intrahepatic cholestasis is long and varied. A number of conditions that typically cause a hepatocellular pattern of injury can also present as a cholestatic variant. Both hepatitis B and C viruses can cause cholestatic hepatitis (fibrosing cholestatic hepatitis). This disease variant has been reported in patients who have undergone solid organ transplantation. Hepatitis A and E, alcoholic hepatitis, and EBV or CMV infections may also present as cholestatic liver disease.

Drugs may cause intrahepatic cholestasis that is usually reversible after discontinuation of the offending agent, although it may take many months for cholestasis to resolve. Drugs most commonly associated with cholestasis are the anabolic and contraceptive steroids. Cholestatic hepatitis has been reported with chlorpromazine, imipramine, tolbutamide, sulindac, cimetidine, and erythromycin estolate. It also occurs in patients taking trimethoprim; sulfamethoxazole; and penicillin-based antibiotics such as ampicillin, dicloxacillin, and clavulanic acid. Rarely, cholestasis may be chronic and associated with progressive fibrosis despite early discontinuation of the offending drug. Chronic cholestasis has been associated with chlorpromazine and prochlorperazine.

Primary biliary cirrhosis is an autoimmune disease predominantly affecting middle-aged women and characterized by progressive destruction of interlobular bile ducts. The diagnosis is made by the detection of antimitochondrial antibody, which is found in 95% of patients.

Primary sclerosing cholangitis is characterized by the destruction and fibrosis of larger bile ducts. The diagnosis of PSC is made with cholangiography (either MRCP or ERCP), which demonstrates the pathognomonic segmental strictures. Approximately 75% of patients with PSC have inflammatory bowel disease.

The vanishing bile duct syndrome and adult bile ductopenia are rare conditions in which a decreased number of bile ducts are seen in liver biopsy specimens. The histologic picture is similar to that in primary biliary cirrhosis. This picture is seen in patients who develop chronic rejection after liver transplantation and in those who develop graft-versus-host disease after bone marrow transplantation. Vanishing bile duct syndrome also occurs in rare cases of sarcoidosis, in patients taking certain drugs (including chlorpromazine), and idiopathically.

There are also familial forms of intrahepatic cholestasis. The familial intrahepatic cholestatic syndromes include progressive familial intrahepatic cholestasis (PFIC) types 1–3 and benign recurrent cholestasis (BRC). PFIC1 and BRC are autosomal recessive diseases that result from mutations in the ATP8B1 gene that encodes a protein belonging to the subfamily of P-type ATPases; the exact function of this protein remains poorly defined. While PFIC1 is a progressive condition that manifests in childhood, BRC presents later and is marked by recurrent episodes of jaundice and pruritus; the episodes are self-limited but can be debilitating. PFIC2 is caused by mutations in the ABCB11 gene, which encodes the bile salt export pump, and PFIC3 is caused by mutations in the multidrug-resistant P-glycoprotein 3. Cholestasis of pregnancy occurs in the second and third trimesters and resolves after delivery. Its cause is unknown, but the condition is probably inherited, and cholestasis can be triggered by estrogen administration.

Other causes of intrahepatic cholestasis include total parenteral nutrition (TPN); nonhepatobiliary sepsis; benign postoperative cholestasis; and a paraneoplastic syndrome associated with a number of different malignancies, including Hodgkin's disease, medullary thyroid cancer, renal cell cancer, renal sarcoma, T cell lymphoma, prostate cancer, and several gastrointestinal malignancies. The term Stauffer's syndrome has been used for intrahepatic cholestasis specifically associated with renal cell cancer. In patients developing cholestasis in the intensive care unit, the major considerations should be sepsis, ischemic hepatitis ("shock liver"), and TPN jaundice. Jaundice occurring after bone marrow transplantation is most likely due to

veno-occlusive disease or graft-versus-host disease. In addition to hemolysis, sickle cell disease may cause intrahepatic and extrahepatic cholestasis. Jaundice is a late finding in heart failure caused by hepatic congestion and hepatocellular hypoxia. Ischemic hepatitis is a distinct entity of acute hypoperfusion characterized by an acute and dramatic elevation in the serum aminotransferases followed by a gradual peak in serum bilirubin.

Jaundice with associated liver dysfunction can be seen in severe cases of *Plasmodium falciparum* malaria. The jaundice in these cases is due to a combination of indirect hyperbilirubinemia from hemolysis and both cholestatic and hepatocellular jaundice. Weil's disease, a severe presentation of leptospirosis, is marked by jaundice with renal failure, fever, headache, and muscle pain.

Causes of extrahepatic cholestasis can be split into malignant and benign. Malignant causes include pancreatic, gallbladder, and ampullary cancers as well as cholangiocarcinoma. This last malignancy is most commonly associated with PSC and is exceptionally difficult to diagnose because its appearance is often identical to that of PSC. Pancreatic and gallbladder tumors as well as cholangiocarcinoma are rarely resectable and have poor prognoses. Ampullary carcinoma has the highest surgical cure rate of all the tumors that present as painless jaundice. Hilar lymphadenopathy due to metastases from other cancers may cause obstruction of the extrahepatic biliary tree.

Choledocholithiasis is the most common cause of extrahepatic cholestasis. The clinical presentation can range from mild right-upper-quadrant discomfort with only minimal elevations of enzyme test values to ascending cholangitis with jaundice, sepsis, and circulatory collapse. PSC may occur with clinically important strictures limited to the extrahepatic biliary tree. IgG4-associated cholangitis is marked by stricturing of the biliary tree. It is critical that the clinician differentiate this condition from PSC as it is responsive to glucocorticoid therapy. In rare instances, chronic pancreatitis causes strictures of the distal common bile duct, where it passes through the head of the pancreas. AIDS cholangiopathy is a condition that is usually due to infection of the bile duct epithelium with CMV or cryptosporidia and has a cholangiographic appearance similar to that of PSC. The affected patients usually present with greatly elevated serum alkaline phosphatase levels (mean, 800 IU/L), but the bilirubin level is often near normal. These patients do not typically present with jaundice.

## CHRONIC CHOLECYSTITIS

**Definition.** Chronic cholecystitis is an inflammation of the gallbladder with the presence of gallbladder-related symptoms because of motor dysfunction and changes in chemical and physical bile content (dyscholia). Cholesterosis may be present, with deposits of cholesterol in the mucosa and muscle layers of the gallbladder.

### Classification.

- calculous/acalculous;
- with dyskinesia of hyperkinetic/hypokinetic/mixed type;
- severity mild/moderate/severe;
- period of exacerbation/remission.

**Epidemiology.** In 5–10% of patients with cholecystitis, calculi obstructing the cystic duct are not found at surgery. In >50% of such cases, an underlying explanation for acalculous inflammation is not found. Affected patients are often young and female

**Etiological factors and risk factors.** The main etiological factor is an infection (staphylococcus, *Proteus*, *Clostridia*, *Escherichia coli*). The presence of bacteria in the bile occurs in >25% of patients with chronic cholecystitis. Additional factors include stress, functional disorders of gallbladder and bile ducts, endocrine diseases.

Risk factors are: fasting, total parenteral nutrition, septicemia, biliary infections, major trauma, burns, major nonbiliary surgery, childbirth, multiple blood transfusions, mechanical

ventilation, opiates, immunosuppression—chemotherapy, HIV infection, transplantation, diabetes, ischemic heart disease, malignancy.

**Pathogenesis.**Inflammatory response can be evoked by three factors: mechanical inflammation produced by increased intraluminal pressure and distention with resulting ischemia of the gallbladder mucosa and wall, chemical inflammation caused by the release of lysolecithin (due to the action of phospholipase on lecithin in bile) and other local tissue factors, and bacterial inflammation, which may play a role in 50–85% of patients with cholecystitis. The organisms most frequently isolated by culture of gallbladder bile in these patients include *Escherichia coli*, *Klebsiella* spp., *Streptococcus* spp., and *Clostridium* spp. Infection can get the gallbladder from intestine, blood, by lymphatic system. Neuroendocrine lesions lead to motoric changes of gallbladder and releases in bile content changes and its stagnation.

**Clinical features.**As with biliary colic, the pain of cholecystitis localizes in abdominal right upper quadrant (RUQ) may radiate to the interscapular area, right scapula, or shoulder. The pain can be caused by roasted, fatty meal. Nausea and vomiting are relatively common and may produce symptoms and signs of vascular and extracellular volume depletion. Jaundice may occur when edematous inflammatory changes involve the bile ducts and surrounding lymph nodes. A low-grade fever is characteristically present, but shaking chills or rigors are not uncommon. Bitter taste in mouth, bloating and changes in feces can be present.

**Diagnosis.**The diagnosis of cholecystitis is usually made on the basis of a characteristic history and physical examination. The patient is anorectic and often nauseated. The RUQ of the abdomen is almost invariably tender to palpation. An enlarged, tense gallbladder is palpable in 25–50% of patients. Deep inspiration or cough during subcostal palpation of the RUQ usually produces increased pain and inspiratory arrest (Murphy's sign). Pain in point of Ker, positive symptoms of Ortner, Georhievsky-Myssi can be found. Localized rebound tenderness in the RUQ is common.

The triad of sudden onset of RUQ tenderness, fever, and leukocytosis is highly suggestive. Typically, leukocytosis in the range of 10,000–15,000 cells per microliter with a left shift on differential count is found. The serum bilirubin is mildly elevated ( $<85.5 \mu\text{mol/L}$  [ $5 \text{ mg/dL}$ ]) in fewer than half of patients, whereas about one-fourth have modest elevations in serum aminotransferases (usually less than a fivefold elevation). Ultrasound will demonstrate calculi in 90–95% of cases and is useful for detection of signs of gallbladder inflammation including thickening of the wall, pericholecystic fluid, and dilatation of the bile duct. The radionuclide (e.g., HIDA) biliary scan may be confirmatory if bile duct imaging is seen without visualization of the gallbladder.

Mirizzi's syndrome is a rare complication in which a gallstone becomes impacted in the cystic duct or neck of the gallbladder causing compression of the CBD, resulting in CBD obstruction and jaundice. Ultrasound shows gallstone(s) lying outside the hepatic duct. Endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or magnetic resonance cholangiopancreatography (MRCP) will usually demonstrate the characteristic extrinsic compression of the CBD.

Although the clinical manifestations of acalculous cholecystitis are indistinguishable from those of calculous cholecystitis, the setting of acute gallbladder inflammation complicating severe underlying illness is characteristic of acalculous disease. Ultrasound or computed tomography (CT) examinations demonstrating a large, tense, static gallbladder without stones and with evidence of poor emptying over a prolonged period may be diagnostically useful in some cases.

Biliary dyskinesia may be diagnosed by food-cholecystokinin-stimulated US or a HIDA scan.

**Complications.**Empyema, gangrene, perforation, fistula, gallstone ileus, cholangitis, pancreatitis, etc.

**Differential diagnosis.**Hepatobiliary disorders, including cholecystitis and biliary colic, may mimic acute cardiopulmonary diseases. Although the pain arising from thesegastrointestinal disorders usually localizes to the right upper quadrant of the abdomen, it is variable and may be felt in the epigastrium and radiate to the back and lower chest. This discomfort is sometimes referred to the scapula or may in rare cases be felt in the shoulder, suggesting diaphragmatic irritation. The pain is steady, usually lasts several hours, and subsides spontaneously, without symptoms between attacks.

Radioisotopic hepatobiliary iminodiacetic acid scans (HIDAs) may help differentiate cholecystitis or biliary colic from pancreatitis. ACT scan may demonstrate an enlarged pancreas, ruptured spleen, or thickened colonic or appendiceal wall, etc.

**Treatment.**In 80 to 90% of patients with abnormal stimulated motility, symptoms are relieved by cholecystectomy.Although surgical intervention remains the mainstay of therapy for acute cholecystitis or chronic cholecystitis with often periods of exacerbation and its complications, a period of in-hospital stabilization may be required before cholecystectomy. Meperidine or nonsteroidal anti-inflammatory drugs (NSAIDs) are usually employed for analgesia because they may produce less spasm of the sphincter of Oddi than drugs such as morphine. Antibiotic therapy is usually indicated in patients, even though bacterial superinfection of bile may not have occurred in the early stages of the inflammatory process. Antibiotic therapy is guided by the most common organisms likely to be present, which are *E. coli*, *Klebsiella* spp., and *Streptococcus* spp. Effective antibiotics include ureidopenicillins such as piperacillin or mezlocillin, ampicillin sulbactam, ciprofloxacin, moxifloxacin, and third-generation cephalosporins. Anaerobic coverage by a drug such as metronidazole should be added. Imipenem and meropenem represent potent parenteral antibiotics that cover the whole spectrum of bacteria causing ascending cholangitis. They should, however, be reserved for the most severe, life-threatening infections when other regimens have failed.

The optimal timing of surgical intervention in patients with cholecystitis depends on stabilization of the patient. Urgent (emergency) cholecystectomy or cholecystostomy is probably appropriate in most patients in whom a complication of cholecystitis such as empyema, emphysematous cholecystitis, or perforation is suspected or confirmed. Patients with uncomplicated acute cholecystitis should undergo early elective laparoscopic cholecystectomy, ideally within 48–72 h after diagnosis.

## CHOLELITHIASIS

**Definition and classification.** There are three different types of gallstones: cholesterol gallstones, mixed gallstones, and pigment stones, which can be further divided into black and brown stones. Cholesterol and mixed stones account for 80% of gallstone disease. Cholesterol stones contain more than 70% cholesterol, whereas mixed stones also contain significant amounts of pigments such as bilirubin. Black pigment stones, which are generally associated with hemolytic diseases, contain calcium salts, bilirubin, and proteins. Brown pigment stones are associated with intrahepatic cholangitis and infection; brown stones are seen after cholecystectomy, especially when they manifest as choledocholithiasis.

**Epidemiology.** Gallstones are quite prevalent in most Western countries. Gallstone formation increases after age 50. In the United States, the third National Health and Nutrition Examination Survey (NHANES III) has revealed an overall prevalence of gallstones of 7.9% in men and 16.6% in women. The prevalence was high in Mexican Americans (8.9% in men,

26.7% in women), intermediate for non-Hispanic whites (8.6% in men, 16.6% in women), and low for African Americans (5.3% in men, 13.9% in women).

**Etiology and pathogenesis.** Gallstones are formed because of abnormal bile composition. They are divided into two major types: cholesterol stones and pigment stones. Pigment stones are composed primarily of calcium bilirubinate; they contain <20% cholesterol and are classified into “black” and “brown” types, the latter forming secondary to chronic biliary infection. Cholesterol is essentially water insoluble and requires aqueous dispersion into either micelles or vesicles, both of which require the presence of a second lipid to solubilize the cholesterol. Cholesterol and phospholipids are secreted into bile as unilamellar bilayered vesicles, which are converted into mixed micelles consisting of bile acids, phospholipids, and cholesterol by the action of bile acids. If there is an excess of cholesterol in relation to phospholipids and bile acids, unstable, cholesterol-rich vesicles remain, which aggregate into large multilamellar vesicles from which cholesterol crystals precipitate.

There are several important mechanisms in the formation of lithogenic (stone-forming) bile. The most important is increased biliary secretion of cholesterol. This may occur in association with obesity, the metabolic syndrome, high-caloric and cholesterol-rich diets, or drugs (e.g., clofibrate) and may result from increased activity of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of hepatic cholesterol synthesis, and increased hepatic uptake of cholesterol from blood. In addition to environmental factors such as high-caloric and cholesterol-rich diets, genetic factors play an important role in gallstone disease. A single nucleotide polymorphism of the gene encoding the hepatic cholesterol transporter ABCG5/G8 has been found in 21% of patients with gallstones, but only in 9% of the general population. It is thought to cause a gain of function of the cholesterol transporter and to contribute to cholesterol hypersecretion.

An additional disturbance of bile acid metabolism that is likely to contribute to supersaturation of bile with cholesterol is enhanced conversion of cholic acid to deoxycholic acid, with replacement of the cholic acid pool by an expanded deoxycholic acid pool. It may result from enhanced dehydroxylation of cholic acid and increased absorption of newly formed deoxycholic acid. An increased deoxycholate secretion is associated with hypersecretion of cholesterol into bile. While supersaturation of bile with cholesterol is an important prerequisite for gallstone formation, it is generally not sufficient by itself to produce cholesterol precipitation *in vivo*. Most individuals with supersaturated bile do not develop stones because the time required for cholesterol crystals to nucleate and grow is longer than the time bile remains in the gallbladder. An important mechanism is nucleation of cholesterol monohydrate crystals, which is greatly accelerated in human lithogenic bile. Accelerated nucleation of cholesterol monohydrate in bile may be due to either an excess of pronucleating factors or a deficiency of antinucleating factors. Mucin and certain nonmucin glycoproteins, principally immunoglobulins, appear to be pronucleating factors, while apolipoproteins A-I and A-II and other glycoproteins appear to be antinucleating factors. Pigment particles may possibly play a role as nucleating factors. In a genome-wide analysis of serum bilirubin levels, the uridine diphosphate-glucuronyltransferase 1A1 (UGT1A1).

Gilbert's syndrome gene variant was associated with the presence of gallstone disease. Because most gallstones associated with the UGT1A1 variant were cholesterol stones, this finding points to the role of pigment particles in the pathogenesis of gallbladder stones. Cholesterol monohydrate crystal nucleation and crystal growth probably occur within the mucin gel layer. Vesicle fusion leads to liquid crystals, which, in turn, nucleate into solid cholesterol monohydrate crystals. Continued growth of the crystals occurs by direct nucleation of cholesterol molecules from supersaturated unilamellar or multilamellar biliary vesicles.

A third important mechanism in cholesterol gallstone formation is gallbladder hypomotility. If the gallbladder emptied all supersaturated or crystal-containing bile completely, stones would not be able to grow. The incidence of gallstones is increased in conditions associated with infrequent or impaired gallbladder emptying such as fasting, parenteral nutrition, or pregnancy and in patients using drugs that inhibit gallbladder motility. Biliary sludge is a thick, mucous material that, upon microscopic examination, reveals lecithin-cholesterol liquid crystals, cholesterol monohydrate crystals, calcium bilirubinate, and mucin gels. Biliary sludge typically forms a crescent-like layer in the most dependent portion of the gallbladder and is recognized by characteristic echoes on ultrasonography. The presence of biliary sludge implies two abnormalities: the normal balance between gallbladder mucin secretion and elimination has become deranged, and nucleation of biliary solutes has occurred. That biliary sludge may be a precursor form of gallstone disease is evident from several observations. It should be emphasized that biliary sludge can develop with disorders that cause gallbladder hypomotility; i.e., surgery, burns, total parenteral nutrition, pregnancy, and oral contraceptives—all of which are associated with gallstone formation. However, the presence of biliary sludge implies supersaturation of bile with either cholesterol or calcium bilirubinate. Two other conditions are associated with cholesterol-stone or biliary-sludge formation: pregnancy and rapid weight reduction through a very-low-calorie diet. There appear to be two key changes during pregnancy that contribute to a “cholelithogenic state”: a marked increase in cholesterol saturation of bile during the third trimester and sluggish gallbladder contraction in response to a standard meal, resulting in impaired gallbladder emptying.

To summarize, cholesterol gallstone disease occurs because of several defects, which include bile supersaturation with cholesterol, nucleation of cholesterol monohydrate with subsequent crystal retention and stone growth, and abnormal gallbladder motor function with delayed emptying and stasis.

Black pigment stones are composed of either pure calcium bilirubinate or polymer-like complexes with calcium and mucin glycoproteins. They are more common in patients who have chronic hemolytic states (with increased conjugated bilirubin in bile), liver cirrhosis, Gilbert’s syndrome, or cystic fibrosis. Gallbladder stones in patients with ileal diseases, ileal resection, or ileal bypass generally are also black pigment stones. Enterohepatic recycling of bilirubin in ileal disease states contributes to their pathogenesis.

Brown pigment stones are composed of calcium salts of unconjugated bilirubin with varying amounts of cholesterol and protein. They are caused by the presence of increased amounts of unconjugated, insoluble bilirubin in bile that precipitates to form stones. Deconjugation of an excess of soluble bilirubin mono- and diglucuronides may be mediated by endogenous  $\beta$ -glucuronidase but may also occur by spontaneous hydrolysis. Sometimes, the enzyme is also produced when bile is chronically infected by bacteria, and such stones are brown. Pigment stone formation is frequent in Asia and is often associated with infections in the gallbladder and biliary tree.

**Clinical features.** Gallstones usually produce symptoms by causing inflammation or obstruction following their migration into the cystic duct or common bile duct (CBD). The most specific and characteristic symptom of gallstone disease is biliary colic that is a constant and often long-lasting pain. Obstruction of the cystic duct or CBD by a stone produces increased intraluminal pressure and distention of the viscus that cannot be relieved by repetitive biliary contractions. The resultant visceral pain is characteristically a severe, steady ache or fullness in the epigastrium or right upper quadrant (RUQ) of the abdomen with frequent radiation to the interscapular area, right scapula, or shoulder. Biliary colic begins quite suddenly and may persist with severe intensity for 30 min to 5 h, subsiding gradually or rapidly. An episode of biliary pain

persisting beyond 5 h should raise the suspicion of acute cholecystitis. Nausea and vomiting frequently accompany episodes of biliary pain. An elevated level of serum bilirubin and/or alkaline phosphatase suggests a common duct stone. Fever or chills (rigors) with biliary pain usually imply a complication, i.e., cholecystitis, pancreatitis, or cholangitis. Complaints of short-lasting, vague epigastric fullness, dyspepsia, eructation, or flatulence, especially following a fatty meal, should not be confused with biliary pain. Such symptoms are frequently elicited from patients with or without gallstone disease but are not specific for biliary calculi. Biliary colic may be precipitated by eating a fatty meal, by consumption of a large meal following a period of prolonged fasting, or by eating a normal meal; it is frequently nocturnal, occurring within a few hours of retiring. The characteristic presentation also involves biliary jaundice.

**Diagnosis.** Ultrasonography of the gallbladder is very accurate in the identification of cholelithiasis and has replaced oral cholecystography. Stones as small as 1.5 mm in diameter may be confidently identified provided that firm criteria are used (e.g., acoustic “shadowing” of opacities that are within the gallbladder lumen and that change with the patient’s position, by gravity). Biliary sludge is material of low echogenic activity that typically forms a layer in the most dependent position of the gallbladder. This layer shifts with postural changes but fails to produce acoustic shadowing; these two characteristics distinguish sludges from gallstones. Ultrasound can also be used to assess the emptying function of the gallbladder.

The plain abdominal film may detect gallstones containing sufficient calcium. Plain radiography may also be of use in the diagnosis of emphysematous cholecystitis, porcelain gallbladder, limey bile, and gallstone ileus.

Oral cholecystography (OCG) has historically been a useful procedure for the diagnosis of gallstones but has been replaced by ultrasound and is regarded as obsolete. It may be used to assess the patency of the cystic duct and gallbladder emptying function. Further, OCG can also delineate the size and number of gallstones and determine whether they are calcified. Radiopharmaceuticals such as  $^{99m}\text{Tc}$ -labeled N-substituted iminodiacetic acids (HIDA, DIDA, DISIDA, etc.) are rapidly extracted from the blood and are excreted into the biliary tree in high concentration even in the presence of mild to moderate serum bilirubin elevations. Failure to image the gallbladder in the presence of biliary ductal visualization may indicate cystic duct obstruction, acute or chronic cholecystitis, or surgical absence of the organ. Such scans have some application in the diagnosis of acute cholecystitis.

**Complications.** Acute cholecystitis, which is the most common serious complication of gallstone disease, can lead to perforation of the gallbladder, peritonitis, fistula into the intestine or duodenum with gallstone ileus or obstruction, and abscesses in the liver or abdominal cavity. Acute cholecystitis is caused by obstruction of the cystic duct, and the ensuing increased intraluminal pressure can lead to vascular compromise of the gallbladder. *Salmonella* and other less common microorganisms such as *Vibrio cholerae*, *Leptospira*, and *Listeria* can cause primary cholecystitis.

**Treatment.** In asymptomatic gallstone patients, the risk of developing symptoms or complications requiring surgery is quite small. Thus, a recommendation for cholecystectomy in a patient with gallstones should probably be based on assessment of three factors: the presence of symptoms that are frequent enough or severe enough to interfere with the patient’s general routine; the presence of a prior complication of gallstone disease, i.e., history of acute cholecystitis, pancreatitis, gallstone fistula, etc.; or the presence of an underlying condition predisposing the patient to increased risk of gallstone complications (e.g., calcified or porcelain gallbladder and/or a previous attack of acute cholecystitis regardless of current symptomatic status). Patients with very large gallstones (>3 cm in diameter) and patients harboring gallstones in a congenitally anomalous gallbladder might also be considered for prophylactic cholecystectomy. Laparoscopic cholecystectomy is a minimal access approach for the removal of

the gallbladder together with its stones. Its advantages include a markedly shortened hospital stay, minimal disability, and decreased cost, and it is the procedure of choice for most patients referred for elective cholecystectomy. Laparoscopic cholecystectomy has become the “gold standard” for treating symptomatic cholelithiasis.

Stone dissolution carefully can be performed in selected patients with a functioning gallbladder and with radiolucent stones <10 mm in diameter. For good results within a reasonable time period, this therapy should be limited to radiolucent stones smaller than 5 mm in diameter. The dose of ursodeoxycholic acid (UDCA) should be 10–15 mg/kg per day. Stones larger than 10 mm in size rarely dissolve. Pigment stones are not responsive to UDCA therapy. However, in addition to the vexing problem of recurrent stones (30–50% over 3–5 years of follow-up), there is also the factor of taking an expensive drug for up to 2 years. The advantages and success of laparoscopic cholecystectomy have largely reduced the role of gallstone dissolution to patients who wish to avoid or are not candidates for elective cholecystectomy. However, patients with cholesterol gallstone disease who develop recurrent choledocholithiasis after cholecystectomy should be on long-term treatment with UDCA.

## **FUNCTIONAL BILIARY DISORDERS**

The concept that disordered function of the gallbladder (GB) and sphincter of Oddi (SO) can cause pain is based mainly on the fact that many patients have biliary-type pain in the absence of recognized organic causes, and that some apparently are cured by removal of the GB or ablation of the sphincter.

**Diagnostic Criteria for Biliary Pain.** Pain located in the epigastrium and/or right upper quadrant and all of the following:

1. Builds up to a steady level and lasting 30 minutes or longer
2. Occurring at different intervals (not daily)
3. Severe enough to interrupt daily activities or lead to an emergency department visit
4. Not significantly (<20%) related to bowel movements
5. Not significantly (<20%) relieved by postural change or acid suppression

Supportive Criteria: The pain may be associated with:

1. Nausea and vomiting
2. Radiation to the back and/or right infrascapular region
3. Waking from sleep

**Definition.** In conformity with the Rome consensus IV that defines functional gastrointestinal disorders as symptom complexes not explained by a clearly identified mechanism or by a structural alteration, we use the term functional gallbladder disorder (FGBD) to describe patients with biliary pain and an intact GB without stones or sludge.

### **Classification.**

- Functional Gallbladder Disorder
- Functional Biliary Sphincter Disorder
- Functional Pancreatic Sphincter Dysfunction

**Epidemiology.** Biliary pain is a common clinical problem, and cholecystectomy is a frequent operation. The number and proportion done for FGBD seems to be increasing in the United States, where case series now list it as the indication for cholecystectomy in 10%-20% of adults and in 10%-50% of children. FGBD is rarely diagnosed outside the United States.

### **Functional Gallbladder Disorder**

#### **Diagnostic Criteria for Functional Gallbladder Disorder:**



1. Biliary pain
  2. Absence of gallstones or other structural pathology
- Supportive Criteria:
1. Low ejection fraction on gallbladder scintigraphy
  2. Normal liver enzymes, conjugated bilirubin, and amylase/lipase

**Pathogenesis.** FGBD is often diagnosed by a low gallbladder ejection fraction (GBEF) at cholecystokinin-stimulated cholescintigraphy (CCK-CS). Although the relationship between GBEF and clinical outcome remains unclear, gallbladder dysmotility may still play a role in the pathogenesis of symptoms, by promoting gallbladder inflammation, which is commonly found. Microlithiasis is associated with a delayed ejection fraction on scintigraphy. Investigators have found multiple defects in gallbladder contractility, including spontaneous activity and abnormal responses to both CCK and neural stimulation. A vicious cycle of stasis and inflammation exists in the GB. Some patients may have intrinsic defects in contractility, and subtle defects in bile composition may also play a role. Studies have shown elevated sphincter of Oddi (SO) pressures in patients with GB dyskinesia, but without correlation between GBEF and SO pressure. GB dysfunction may represent a more generalized dysmotility, as in irritable bowel syndrome and chronic constipation, and perhaps gastroparesis. Experimental evidence has implicated several molecules that can link inflammation to motility, the most important of which may be prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).

**Diagnosis.** GB stones should be excluded by ultrasound scanning (repeated if necessary), and complemented with EUS. Other tests may be needed to rule out peptic ulcer disease, subtle chronic pancreatitis, fatty liver disease, or musculoskeletal syndromes. Esophageal manometry, gastric emptying tests, and transit studies may be required if symptoms suggest alternative dysfunctional syndromes. Further management depends on the level of clinical suspicion. The diagnosis of FGBD may be made by exclusion if the pains are typical and severe. A key issue is whether current methods for assessing GB muscular function are useful.

CCK-CS is a popular diagnostic test, but its value is controversial. The test involves the intravenous administration of technetium 99m (Tc 99m) labeled hepatobiliary iminodiacetic acid analogs. These compounds are readily excreted into the biliary tract, and are concentrated in the GB. The net activity-time curve for the GB is derived from serial observations, and GB emptying is expressed as the GBEF, which is the percentage change of net GB counts. An interdisciplinary panel proposed a standardized test and emphasized that proper patient selection is a critical step when considering whether to perform CCK-CS, because delayed emptying is seen in many other conditions, including asymptomatic individuals and patients with other functional gastrointestinal disorders. The injection of CCK can cause biliary-like pain, but using this observation to determine patient-care decisions was discouraged by the panel, because CCK also increases bowel motility, which can cause symptoms. In some countries, CCK preparations have not been approved for human use.

GB emptying can be assessed with ultrasound scanning after CCK or fatty meal stimulation, but these methods have not become popular. Attempts are being made to study emptying patterns during magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) scanning with results that appear to mimic those of cholescintigraphy.

**Treatment.** Symptoms suggestive of FGBD often resolve spontaneously, so that early intervention is unwarranted. Patients may respond to reassurance and medical treatments such as antispasmodics, neuromodulators, or ursodeoxycholic acid, although their value has not been evaluated formally.

Cholecystectomy is considered when these methods fail, and symptoms are severe. The reported results of surgery vary widely. Many claim benefit in >80% of patients, but most studies

are of poor quality with several potential biases; none have limited intervention to patients with negative EUS exams. However, cholecystectomy is claimed to benefit most patients with “typical biliary” symptoms, raising the question as to what additional utility is afforded by CCK-CS. One study reported symptomatic relief after cholecystectomy in 94% of patients with a low GBEF, but also in 85% of those with a normal GBEF. That many patients with suspected FGBD are not helped by cholecystectomy is shown by the significant number who present afterward with “postcholecystectomy pain,” and are considered for another contentious diagnosis, sphincter of Oddi dysfunction (SOD).

### **Functional Biliary Sphincter Disorder**

#### **Diagnostic Criteria for Functional Biliary Sphincter of Oddi Disorder:**

1. Criteria for biliary pain
2. Elevated liver enzymes or dilated bile duct, but not both
3. Absence of bile duct stones or other structural abnormalities

#### **Supportive Criteria**

1. Normal amylase/lipase
2. Abnormal sphincter of Oddi manometry
3. Hepatobiliary scintigraphy

**Pathogenesis.** Classical teaching is that aberrant sphincter physiology leads to biliary pain by increased resistance to bile outflow and subsequent rise in intrabiliary pressure. This concept is intuitively appealing, leading to widespread acceptance, especially by biliary endoscopists. However, both theoretical and experimental evidence indicate a more complex pathophysiology. There is evidence that sphincter dynamics are altered after cholecystectomy. Animal studies have shown a cholecystosphincteric reflex with distention of the GB that results in sphincter relaxation. Interruption of this reflex could affect sphincter behavior by an altered response to CCK, or because the loss of innervation unmask the direct contractile effects of CCK on smooth muscle.

Abnormalities in both basal pressure and responsiveness to CCK have also been described in humans. The simple concept of SOD leading to obstruction and biliary pain is now being challenged. One explanation for this syndrome stems from the concept of nociceptive sensitization. Significant tissue inflammation, such as cholecystitis, will activate nociceptive neurons acutely and, if it persists, will also result in sensitization and the gain in the entire pain pathway is increased. In most patients with GB disease, cholecystectomy removes the ongoing stimulus and the system reverts back to its normal state. However, in a subset of patients, the “gain” stays at a high level. In such patients, even minor increases in biliary pressure (within the physiological range) can trigger nociceptive activity and the sensation of pain (allodynia).

A relevant related phenomenon is cross-sensitization. Many viscera share sensory innervation. For example, nearly half of the sensory neurons in the pancreas also innervate the duodenum. Therefore, it is difficult to distinguish pain resulting in one organ from that in another. Persistent sensitization in one organ can lead to sensitization of the nociceptive pathway from an adjacent organ. Thus, an entire region can be sensitized with innocuous stimuli (such as duodenal contraction after a meal) leading to pain that was indistinguishable from that associated with the initial insult.

Motor phenomena, such as sphincter hypertension, might still be relevant, but more as a marker for the syndrome rather than the cause.

**Diagnosis.** The first task in patients with post-cholecystectomy pain is to exclude organic causes. Possibilities include retained stones or partial GB; postoperative complications (such as a bile leak or duct stricture); other intra-abdominal disorders, such as pancreatitis, fatty liver

disease, peptic ulceration, functional dyspepsia and irritable bowel syndrome; musculoskeletal disorders; and other rare conditions.

Nonbiliary findings are more likely when the symptoms are atypical and longstanding, similar to those suffered preoperatively and without a period of relief postoperatively, and when the GB did not contain stones. The initial diagnostic approach should consist of a careful history and physical examination, followed by standard liver and pancreas blood tests, upper endoscopy, and abdominal imaging. Although ultrasound or computed tomography scanning may be used initially, MRCP or EUS provide more complete information.

The report of a “dilated bile duct” on any of these studies is difficult to interpret. It is widely believed that the bile duct enlarges after cholecystectomy. However, some studies have shown no change, others only a slight increase in size; there is a gradual increase with age. Regular narcotic use can cause biliary dilation, although usually associated with normal liver enzymes. EUS is the best way to rule out duct stones and pathology of the papilla.

A major problem with assessing diagnostic tools in this context is the lack of a gold standard. One could argue that the only proof that the sphincter is (or was) the cause of the pain is if patients are satisfied by the results of sphincter ablation, albeit recognizing the often prolonged placebo effect of endoscopic retrograde cholangiopancreatography (ERCP) intervention. Many tests are assessed by comparison with the results of manometry, whose validity is also uncertain. Liver enzymes, which peak with attacks of pain, might be a good sign of obstruction by spasm (or passage of stones). Another problem is that most patients have intermittent pains, so that measurements taken when pain-free are open to question. The drainage dynamics of the bile duct have been tested after stimulation with a fatty meal or injection of CCK and measuring any dilatation of the duct with abdominal or endoscopic ultrasound.

Hepatobiliary scintigraphy involves intravenous injection of a radionuclide and deriving time-activity curves for its excretion throughout the hepatobiliary system. This technique has been used to assess the rate of bile flow into the duodenum and to look for any evidence of obstruction. Interpretation of the literature is difficult due to the use of different test protocols, diagnostic criteria, and categories of patients, and whether the results are compared with manometry (usually) or the outcome of sphincterotomy. Various parameters are used: time to peak activity, slope values, and hepatic clearance at predefined time intervals, disappearance time from the bile duct, duodenal appearance time, and the hepatic hilum-duodenum transit time. The reported specificity of hepatobiliary scintigraphy was at least 90% when manometry was used as the reference standard, but the level of sensitivity is more variable.

Endoscopic retrograde cholangiopancreatography and sphincter of Oddi manometry. ERCP should be reserved for patients who need sphincter manometry or endoscopic therapy, such as those with strong objective evidence for biliary obstruction.

ERCP allows measurement of both the biliary and pancreatic sphincters, but the method is imperfect. Recording periods are short and subject to movement artifact.

The assessable variables at SO manometry include the basal sphincter pressure and the phasic wave amplitude, duration, frequency, and propagation pattern. However, only basal pressure has so far been shown to have clinical significance. The standard upper limit of normal for baseline biliary sphincter pressure is 35-40 mm Hg. Normal pancreatic sphincter pressures are accepted as similar to those of the bile duct, although reference data are more limited. For patients in whom the indication for SO manometry is biliary pain and not idiopathic pancreatitis, some authorities avoid pancreatic cannulation entirely to reduce the frequency of pancreatitis.

Sphincter manometry has been recommended in patients with suspected biliary type II SOD because 3 randomized trials showed that biliary manometry predicted the response to biliary sphincterotomy. However, in clinical practice, biliary sphincterotomy is often performed

empirically in those patients. Manometry is no longer recommended in patients without objective findings.

**Treatment.** Many patients are disabled with pain and desperate for assistance.

Because of the risks and uncertainties involved in invasive approaches, it is important to explore conservative management initially. Nifedipine, phosphodiesterase type-5 inhibitors, trimebutine, hyoscine butylbromide, octreotide, and nitric oxide have been shown to reduce basal sphincter pressures in SOD and asymptomatic volunteers during acute manometry. H<sub>2</sub> antagonists, gabexate mesilate, ulinastatin, and gastrokinetic agents also showed inhibitory effects on sphincter motility. Amitriptyline, as a neuromodulator, also has been used along with simple analgesics. A trial of duloxetine had encouraging results. Transcutaneous electrical nerve stimulation and acupuncture also have been shown to reduce SO pressures, but their long-term efficacy has not been evaluated.

Endoscopic therapy: sphincterotomy. Consensus opinion remains that patients with definite evidence for SO obstruction should be treated with endoscopic sphincterotomy without manometry.

Freeman and colleagues showed that normal pancreatic manometry, delayed gastric emptying, daily opioid use, and age younger than 40 years predicted poor outcomes. It has been reported that patients are more likely to respond if their pain was not continuous, if it was accompanied by nausea and vomiting, and if there had been a pain-free interval of at least 1 year after cholecystectomy.

ERCP in patients with SOD (with or without manometry) is associated with a high risk of pancreatitis. The rate is 10%-15%, even in expert hands using pancreatic stent placement and/or rectal nonsteroidal anti-inflammatory drugs.

Sphincterotomy adds the risk of bleeding and retroduodenal perforation, which both occur in about 1% of cases, and also a significant risk for late restenosis, especially after pancreatic sphincterotomy.

Surgical sphincteroplasty can be performed primarily or after failed endoscopic therapy.

### **Functional Pancreatic Sphincter Dysfunction**

#### **Diagnostic Criteria for Pancreatic Sphincter of Oddi Disorder:**

All of the following:

1. Documented recurrent episodes of pancreatitis (typical pain with amylase or lipase >3 times normal and/or imaging evidence of acute pancreatitis)
2. Other etiologies of pancreatitis excluded
3. Negative endoscopic ultrasound
4. Abnormal sphincter manometry

**Pathogenesis.** The idea that dysfunction of the pancreatic sphincter can cause pancreatic pain and pancreatitis is popular. It seems a logical extension to the consensus that sphincter hypertension can cause biliary pain. Obstruction at the sphincter causes pancreatitis in animal experiments, and in several clinical situations, including tumors of the papilla, duct stones, and by mucus plugs in intrapancreatic mucinous neoplasm. In addition, opiates increase sphincter pressure and have been implicated in attacks of pancreatitis. Finally, patients with unexplained attacks of pancreatitis are often found to have elevated pancreatic sphincter pressures.

It remains possible that the finding of sphincter abnormality in these patients is an epiphenomenon, the result of previous attacks, or due to an unexplained cause. The fact that many patients eventually develop features of chronic pancreatitis suggests that the underlying pathogenesis of the disease is not altered.

**Diagnosis.** Measuring the size of the pancreatic duct by MRCP or EUS before and after an intravenous injection of secretin has been used to demonstrate sphincter dysfunction. One report suggests that the results do not correlate with sphincter manometry, but may predict the outcome of sphincterotomy in patients with otherwise unexplained pancreatitis.

**Treatment.** Patients with recurrent acute pancreatitis that remains unexplained after detailed investigation should be reassured that the attacks may stop spontaneously and if they recur, they usually follow the same course and are rarely life threatening. They should be counseled to avoid factors that may precipitate attacks (eg, alcohol, opiates). While certain medications (such as antispasmodics and calcium channel blockers) are known to relax the sphincter, there have been no trials of their use.

In earlier days, cholecystectomy was often recommended after 2 unexplained attacks of pancreatitis, assuming that small stones or microlithiasis were responsible. That approach seems less acceptable now that these are easier to exclude with modern imaging. Others have approached the problem of microlithiasis with biliary sphincterotomy, or treatment with ursodeoxycholic acid.

Pancreatic sphincterotomy would be the logical treatment if the sphincter dysfunction is indeed causative. Historically, complete division of the both sphincters was done by an open transduodenal approach. Case series of patients who have undergone this procedure have claimed resolution of episodic pancreatitis in the majority of patients. The pancreatic sphincterotomies performed endoscopically are much smaller, and repeat manometry studies in patients with recurrent problems often show them to be incomplete.

Manometry has not been repeated in patients without recurrent symptoms, so it is not clear whether treatment has failed because of inadequacy of the sphincterotomy, or an incorrect diagnosis. Stenosis of the pancreatic orifice is not uncommon after pancreatic sphincterotomy, and repeat ERCP treatment rarely resolves the problem.

Endoscopic biliary sphincterotomy is known to reduce pancreatic sphincter pressures in many cases. At the present time, practitioners and patients should approach invasive treatments in this context with considerable caution, recognizing the short and long-term risks, and the marginal evidence for benefit.

## 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),  $\alpha_1$  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-alcoholic 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 coinfect 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: $\beta$ -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, but NASH 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- $\alpha$ . 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 consistent and 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- $\alpha$  (TNF- $\alpha$ ), transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), interleukins 1, 6, 8, and 10, and platelet-derived growth factor (PDGF). TNF- $\alpha$  has plethora of biologic effects and causes hepatocyte apoptosis, whereas TGF- $\beta$ 1 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. For unclear 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- $\alpha$ ) 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 poor appetite, 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  $\gamma$ -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  $\alpha$ -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 1 antibodies 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 hepatitis:

	<b>Antigen(s)</b>	<b>Antibodies</b>	<b>Remarks</b>
<b>HCV</b>	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
<b>HBV</b>	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
<b>HDV</b>	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
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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,  $\alpha$ 1-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  $\gamma$ -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 asymptotically 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 biopsy in 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 viral or 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 $\mu$ mol/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 $\times$ normal elevation	Normal	Usually normal. If >5 $\times$ 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 $\times$ normal elevation	Often decreased	Often prolonged Fails to correct with parenteral

	ria				vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT >2 suggests alcoholic hepatitis or cirrhosis	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to 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)	Bilirubinuria	Rarely >500 IU		Normal	Normal
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation	Elevated, often >4× normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase		

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 (±)	ANA, anti-LKM1 anti-SLAe	Prednisone, azathioprine



	Hyperglobulinemia		
Drug-associated —	-	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 combined with 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 poor tolerability 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 of other inflammatory liver diseases, such as hepatitis C, 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 ( $4.6 \times [\text{patient's prothrombin time} - \text{control prothrombin time}] + \text{total bilirubin level}$ ) 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 resources are 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.

### **Materials for self-control:**

#### **Situation tasks:**

1. Patient K., 34 years old, complains of pain in the right subcostum, which increases after rich and fried meal, bitter taste in mouth, bitter belch. He is considered to be ill for 9 years. Objectively: body overweight, skin of ordinary color. Moderate pain in the right subcostum upon the palpation, positive Myussi-Georgievsky symptom. Liver is not enlarged. Data of the fractional duodenal tubage: bile got in amount of 85 ml during 55 min., at the microscopy - amount of leukocytes is increased. What is the preliminary diagnosis? What additional tests are necessary?
2. A patient, 54 years old, complains of general weakness, absence of appetite, dull pain in the right subcostum, abdominal bloating, weight loss. Lately periodic vomiting with blood appeared. Examination: body weight is reduced, icterus of scleras, skin is dry, "vascular stars" on face and upper extremities, hyperemia of hands, gynecomastia. Tongue is of raspberry colour. Abdomen is enlarged, lower edge of liver is acute, dense, comes from the edge of costal arc on 4 cm. Spleen comes from a costal arc on 6-7 cm. Blood sedimentation is 14 mm/h, thymol test – 8. What is the preliminary diagnosis? What additional tests are necessary?

#### **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 to 37.7°C, 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 gastroenterology department with skin itching, jaundice, discomfort in the right subcostal area, generalized weakness. On examination: skin is jaundiced, 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 Gilbert's icterus
- E. Chronic hepatitis B

4. 36 years old patient complains of frequent pain attacks in the right subcostum, which occurred after childbirth. The day before in the evening she felt acute pain in the right subcostum with radiation to scapula, there was vomiting with bile two times. Body temperature rose to 37,8°C. Examination data: icteric scleras, liver comes from a costal arc on 1 cm, acutely painful gall bladder. What is the most credible diagnosis?

- A. Stricture of biliary tract
- B. Viral hepatitis B
- C. Abscess of liver
- D. Dyskinesia of gall bladder
- E. Exacerbation of chronic cholecystitis

5. Patient with a little body overweight complains of pain in the right subcostum, nausea, periodical vomiting after rich food. From the anamnesis: viral hepatitis A. Objectively: painfulness in the area of the right subcostum, Ker's symptom is positive. The edge of liver comes out of the costal arc on 2 cm. What is the previous diagnosis?

- A. Chronic acalculous cholecystitis
- B. Chronic calculous cholecystitis
- C. Acute cholecystitis
- D. Cholesterosis of gall bladder
- E. Dropsy of gall bladder

6. 50 years old patient complains of pain attacks in the right subcostum, vomiting with bile, nausea. During last 5 years pain in epigastral area was persistent, which was associated with nausea, violations of defecation, dryness in mouth. Objectively: pulse is 92/min., body overweight, tongue is coated with white fur, icteric scleras. Abdomen is soft, painful in the projection of gall bladder, local muscular tension in the right subcostum, positive Ker's symptom. In blood test: L -  $9,6 \times 10^9/l$ , blood sedimentation - 14 mm/h. What is the most credible previous diagnosis?

- A. Cholecystolithiasis
- B. Chronic gastritis, type A
- C. Dyskinesia of biliary tract
- D. Chronic acalculous cholecystitis
- E. Chronic hepatitis

7. 55 years old patient complains of pain attacks in the right subcostum, vomiting with bile, nausea. During last year pain in epigastral area, which was associated with nausea, violations of defecation, dryness in mouth were noticed. Objectively: pulse is 95/min., body overweight, tongue is coated with white fur, icteric scleras. Abdomen is soft, painful in the projection of gall bladder, local muscular tension in the right subcostum, positive Ker's symptom. In blood test: L -  $9,6 \times 10^9/l$ , blood sedimentation - 16 mm/h. What is the most informative method of examination to confirm the diagnosis?

- A. Ultrasonic research of gallbladder
- B. Scintigraphy of liver
- C. Bacteriological research of bile
- D. Cholecystography
- E. Retrograde cholangiopancreatography

8. 32 years old woman noticed periodic attacks of pain in the right subcostum, which can be relieved by no-shpa. Pain is not always related with meal, sometimes it appears at agitation, accompanied with pain in heart, palpitation. Objectively: emotional lability, palpation of abdomen detected painfulness in the area of gall bladder. What is the most reliable diagnosis?

- A. Dyskinesia of biliary tract
- B. Chronic cholecystitis
- C. Chronic cholangitis
- D. Chronic pancreatitis
- E. Duodenitis

9. 49 years old woman visited doctor with complaints on pain attacks of in the right subcostum, nausea. Icterus appeared on the second day. Similar attacks with recurrent icterus repeated twice during last 3 years. Objectively: icteric scleras, tongue is dry, abdomen is bloated, painful in Shoffar's area, positive Ortner's and Ker's symptoms. In blood: L -  $10,0 \times 10^9/l$ , r/n - 16%, blood sedimentation - 25 mm/h. What additional research is it necessary to perform for diagnosis confirmation?

- A. US research of abdominal cavity
- B. Laparoscopy
- C. Duodenal tubage

- D. Cholecystography
- E. Survey roentgenogram of abdominal cavity

10. 48 years old patient complains of pain attacks in the right subcostum after physical work. Periodically notices lighting of feces, darkening of urine. Objectively: skin and mucosa are icteric. Bilirubin: general - 36,8 mkmol/l, direct - 26,4 mkmol/l, indirect - 10,4 mkmol/l. At the US research of gall bladder: thickness of wall is 4 mm, thick bile, echopositive shades - to 4 mm. With litolytic purpose you will prescribe:

- A. Choleric
- B. Ursofalc
- C. Cholekinetic
- D. Spasmolytic
- E. Cytostatic preparations

Correct answers for the situation tasks:

1. Chronic cholecystitis with hypomotoric dyskinesia. US, ERCPG, bacteriological research of bile
2. Liver cirrhosis. Biochemical blood analysis (liver tests), markers of hepatitis in serum, US of abdominal cavity, liver biopsy if necessary.

The answers for the tests:

1-B, 2-B, 3-E, 4-E, 5-A, 6-A, 7-A, 8-A, 9-A, 10-B.

**Recommended literature:**

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