

**Міністерство охорони здоров'я України
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Факультет VI по підготовці іноземних студентів

ЗАТВЕРДЖЕНО

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Зав. кафедри _____ д.мед.н., професор Л.В. Журавльова

**МЕТОДИЧНІ ВКАЗІВКИ
для студентів**

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

Жовчнокам'яна хвороба, хронічний холецистит

та функціональні біліарні порушення

Харків 2016

**KHARKOV NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF INTERNAL MEDICINE N3**

METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

"Gallstone disease, chronic cholecystitis and functional biliary disorders"

Kharkiv 2016

Practical class: “Gallstone disease (GD), chronic cholecystitis (CC) and functional biliary disorders”, 4 hours

The incidence of biliary tract diseases, including GD and chronic cholecystitis is high around the world. GD has not only medical, but also socio-economic importance. The number of patients with biliary tract diseases is almost twice higher than the number of patients with peptic ulcer. The disease occurs 2-3 times more frequently in women than in men. The incidence of gallstone formation in children is less than 5%, whereas in elderly of 60-70 years old it is equal to 30-40%. 80-90% of patients with GD reside in Europe and North America and typically have cholesterol stones, while the population of Asia and Africa tend to have pigment stones.

Learning Objectives:

- To teach students to recognize the major symptoms and syndromes of GD;
- Physical methods of GD investigation;
- Lab and instrumental tests for diagnosis of DG;
- To teach students to interpret the results of additional methods of investigation;
- To teach students to recognize and diagnose GD complications;
- To teach students to prescribe treatment for GD.

What should a student know?

- GD etiological factors;
- GD pathogenesis;
- Main clinical syndromes of GD;
- Clinical signs of GD;
- Methods of physical examination of patients with GD;
- GD diagnosis, evaluation of duodenal intubation (DI) data, including microscopic, bacteriological, biochemical analysis of bile;
- Diagnostic capabilities of endoscopy, plain radiography of the abdomen, endoscopic retrograde cholangiopancreatography, ultrasound of the abdomen, CT, intravenous cholangio-cholecystography, scintigraphy; indications, contraindications for their use;
- Complications of GD;
- GD treatment (lifestyle modification, diet, pharmacological therapy & surgery).

What should a student be able to do?

- To recognize the main clinical and physical syndromes of GD;
- To explain the results of clinical, biochemical and immune-enzyme assays;
- To interpret the data of the following investigations: endoscopy, plain radiography of the abdomen, endoscopic retrograde cholangiopancreatography, ultrasound of the abdomen, endoscopic ultrasound of biliary tract, CT, intravenous cholangio-cholecystography. Indications & contraindications for the use of these methods.
- To interpret the data of microscopic, bacteriological and biochemical studies of bile;
- To be able to identify types of functional biliary tract disorders;
- To prescribe treatment for patients with GD.

The list of practical skills that students should master:

- Examination of skin and mucous membranes;
- Determination of malabsorption syndrome;
- Examination of the abdomen;
- Superficial palpation of the abdomen;
- Profound methodical sliding palpation of the abdomen after Obraztsov-Strazhesko;
- Determination of pain points and areas specific for GD;

Topics contents:

GALLSTONE DISEASE

Cholelithiasis is the medical term for gallstone disease. Cholelithiasis involves the presence of gallstones, which are concretions that form in the biliary tract, usually in the gallbladder. Choledocholithiasis refers to the presence of 1 or more gallstones in the common bile duct (CBD). Gallstones develop insidiously, and they may remain asymptomatic for decades. Migration of a gallstone into the opening of the cystic duct may block the outflow of bile during gallbladder contraction. The resulting increase in gallbladder wall tension produces a characteristic type of pain (biliary colic). Cystic duct obstruction, if it persists for more than a few hours, may lead to acute gallbladder inflammation (acute cholecystitis). Choledocholithiasis refers to the presence of one or more gallstones in the common bile duct. Usually, this occurs when a gallstone passes from the gallbladder into the common bile duct.

Epidemiology

The prevalence of cholelithiasis is affected by many factors, including ethnicity, gender, comorbidities, and genetics.

In the United States, about 20 million people (10-20% of adults) have gallstones. Every year 1-3% of people develop gallstones and about 1-3% of people become symptomatic. Each year, in the United States, approximately 500,000 people develop symptoms or complications of gallstones requiring cholecystectomy. Gallstone disease is responsible for about 10,000 deaths per year in the United States. About 7000 deaths are attributable to acute gallstone complications, such as acute pancreatitis.

Prevalence of gallstones is highest in people of northern European descent, and in Hispanic populations and Native American populations. Prevalence of gallstones is lower in Asians and African Americans. Women are more likely to develop cholesterol gallstones than men, especially during their reproductive years, when the incidence of gallstones in women is 2-3 times that in men. The difference appears to be attributable mainly to estrogen, which increases biliary cholesterol secretion. Risk of developing gallstones increases with age. Gallstones are uncommon in children in the absence of congenital anomalies or hemolytic disorders.

Pathophysiology

Gallstone formation occurs because certain substances in bile are present in concentrations that approach the limits of their solubility. When bile is concentrated in the gallbladder, it can become supersaturated with these substances, which then precipitate from the solution as microscopic crystals. The crystals are trapped in gallbladder mucus, producing gallbladder sludge. Over time, the crystals grow, aggregate, and fuse to form macroscopic stones. Occlusion of the ducts by sludge and/or stones produces the complications of gallstone disease.

The 2 main substances involved in gallstone formation are cholesterol and calcium bilirubinate.

Cholesterol gallstones

More than 80% of gallstones contain cholesterol as their major component. Liver cells secrete cholesterol into bile along with phospholipid (lecithin) in the form of small spherical membranous bubbles, termed unilamellar vesicles. Liver cells also secrete bile salts, which are powerful detergents required for the digestion and absorption of dietary fats.

Bile salts in bile dissolve the unilamellar vesicles to form soluble aggregates called mixed micelles. This happens mainly in the gallbladder, where bile is concentrated by reabsorption of electrolytes and water.

Compared with vesicles (which can hold up to 1 molecule of cholesterol for every molecule of lecithin), mixed micelles have a lower carrying capacity for cholesterol (about 1 molecule of

cholesterol for every 3 molecules of lecithin). If bile contains a relatively high proportion of cholesterol to begin with, then as bile is concentrated, progressive dissolution of vesicles may lead to a state in which the cholesterol-carrying capacity of the micelles and residual vesicles is exceeded. At this point, bile is supersaturated with cholesterol, and cholesterol monohydrate crystals may form.

Thus, the main factors that determine whether cholesterol gallstones will form are (1) the amount of cholesterol secreted by liver cells, relative to lecithin and bile salts, and (2) the degree of concentration and extent of stasis of bile in the gallbladder.

Calcium, bilirubin, and pigment gallstones

Bilirubin, a yellow pigment derived from the breakdown of heme, is actively secreted into bile by liver cells. Most of the bilirubin in bile is in the form of glucuronide conjugates, which are water soluble and stable, but a small proportion consists of unconjugated bilirubin. Unconjugated bilirubin, like fatty acids, phosphate, carbonate, and other anions, tends to form insoluble precipitates with calcium. Calcium enters bile passively along with other electrolytes.

In situations of high heme turnover, such as chronic hemolysis or cirrhosis, unconjugated bilirubin may be present in bile at higher than normal concentrations. Calcium bilirubinate may then crystallize from the solution and eventually form stones. Over time, various oxidations cause the bilirubin precipitates to take on a jet-black color, and stones formed in this manner are termed black pigment gallstones. Black pigment stones represent 10-20% of gallstones.

Bile is normally sterile, but in some unusual circumstances (eg, above a biliary stricture), it may become colonized with bacteria. The bacteria hydrolyze conjugated bilirubin, and the resulting increase in unconjugated bilirubin may lead to precipitation of calcium bilirubinate crystals.

Bacteria also hydrolyze lecithin to release fatty acids, which also may bind calcium and precipitate from the solution. The resulting concretions have a claylike consistency and are termed brown pigment stones. Unlike cholesterol or black pigment gallstones, which form almost exclusively in the gallbladder, brown pigment gallstones often form de novo in the bile ducts. Brown pigment gallstones are unusual in the United States but are fairly common in some parts of Southeast Asia, possibly related to liver fluke infestation.

Mixed gallstones

Cholesterol gallstones may become colonized with bacteria and can elicit gallbladder mucosal inflammation. Lytic enzymes from the bacteria and leukocytes hydrolyze bilirubin conjugates and fatty acids. As a result, over time, cholesterol stones may accumulate a substantial proportion of calcium bilirubinate and other calcium salts, producing mixed gallstones. Large stones may develop a surface rim of calcium resembling an eggshell that may be visible on plain x-ray films.

Etiology

Cholesterol gallstones, black pigment gallstones, and brown pigment gallstones have different pathogeneses and different risk factors.

Cholesterol gallstones

Cholesterol gallstones are associated with female sex, European or Native American ancestry, and increasing age. Other risk factors include the following:

- Obesity
- Pregnancy
- Gallbladder stasis
- Drugs
- Heredity

Black and brown pigment gallstones

Black pigment gallstones occur disproportionately in individuals with high heme turnover. Disorders of hemolysis associated with pigment gallstones include sickle cell anemia, hereditary

spherocytosis, and beta-thalassemia. About half of all cirrhotic patients have pigment gallstones. Prerequisites for the formation of brown pigment gallstones include intraductal stasis and chronic colonization of bile with bacteria. In rice-growing regions of East Asia, infestation with biliary flukes may produce biliary strictures and predispose to formation of brown pigment stones throughout intrahepatic and extrahepatic bile ducts.

Crohn disease, ileal resection, or other diseases of the ileum decrease bile salt reabsorption and increase the risk of gallstone formation.

Other illnesses or states that predispose to gallstone formation include burns, use of total parenteral nutrition, paralysis, ICU care, and major trauma. This is due, in general, to decreased enteral stimulation of the gallbladder with resultant biliary stasis and stone formation.

Clinical presentation

Gallstone disease may be thought of as having the following 4 stages:

- The lithogenic state, in which conditions favor gallstone formation
- Asymptomatic gallstones
- Symptomatic gallstones, characterized by episodes of biliary colic
- Complicated cholelithiasis

Symptoms and complications of gallstone disease result from effects occurring within the gallbladder or from stones that escape the gallbladder to lodge in the common bile duct.

Asymptomatic gallstones

Gallstones may be present in the gallbladder for decades without causing symptoms or complications. In patients with asymptomatic gallstones discovered incidentally, the likelihood of developing symptoms or complications is 1-2% per year. In most cases, asymptomatic gallstones do not require any treatment.

Biliary colic

Pain termed biliary colic occurs when gallstones or sludge fortuitously impact in the cystic duct during a gallbladder contraction, increasing gallbladder wall tension. In most cases, the pain resolves over 30 to 90 minutes as the gallbladder relaxes and the obstruction is relieved.

Episodes of biliary colic are sporadic and unpredictable. The patient localizes the pain to the epigastrium or right upper quadrant and may describe radiation to the right scapular tip (Collins sign^[9]). The pain begins postprandially (usually within an hour after a fatty meal), is often described as intense and dull, and may last from 1-5 hours. From onset, the pain increases steadily over about 10 to 20 minutes and then gradually wanes when the gallbladder stops contracting and the stone falls back into the gallbladder. The pain is constant in nature and is not relieved by emesis, antacids, defecation, flatus, or positional changes. It may be accompanied by diaphoresis, nausea, and vomiting.

Other symptoms, often associated with cholelithiasis, include indigestion, dyspepsia, belching, bloating, and fat intolerance. However, these are very nonspecific and occur in similar frequencies in individuals with and without gallstones; cholecystectomy has not been shown to improve these symptoms.

Distinguishing uncomplicated biliary colic from acute cholecystitis or other complications is important. Key findings that may be noted include the following:

- Uncomplicated biliary colic – Pain that is poorly localized and visceral; an essentially benign abdominal examination without rebound or guarding; absence of fever
- Acute cholecystitis – Well-localized pain in the right upper quadrant, usually with rebound and guarding; positive Murphy sign (nonspecific); frequent presence of fever; absence of peritoneal signs; frequent presence of tachycardia and diaphoresis; in severe cases, absent or hypoactive bowel sounds

The presence of fever, persistent tachycardia, hypotension, or jaundice necessitates a search for complications, which may include the following:

- Cholecystitis
- Cholangitis
- Pancreatitis
- Other systemic causes

Diagnosis

Asymptomatic gallstones are often found incidentally on plain radiographs, abdominal sonograms, or CT scan for workup of other processes. Plain radiographs have little role in the diagnosis of gallstones or gallbladder disease. Cholesterol and pigment stones are radiopaque and visible on radiographs in only 10-30% of instances, depending on their extent of calcification.

Patients with uncomplicated cholelithiasis or simple biliary colic typically have normal laboratory test results; *laboratory studies* are generally not necessary unless complications are suspected. Blood tests, when indicated, may include the following:

- Complete blood count (CBC) with differential
- Liver function panel
- Amylase
- Lipase

Acute cholecystitis is associated with polymorphonuclear leukocytosis. However, up to one third of the patients with cholecystitis may not manifest leukocytosis.

In severe cases, mild elevations of liver enzymes may be caused by inflammatory injury of the adjacent liver.

Choledocholithiasis with acute common bile duct (CBD) obstruction initially produces an acute increase in the level of liver transaminases (alanine and aspartate aminotransferases), followed within hours by a rising serum bilirubin level. The higher the bilirubin level, the greater the predictive value for CBD obstruction. CBD stones are present in approximately 60% of patients with serum bilirubin levels greater than 3 mg/dL.

If obstruction persists, a progressive decline in the level of transaminases with rising alkaline phosphatase and bilirubin levels may be noted over several days. Prothrombin time may be elevated in patients with prolonged CBD obstruction, secondary to depletion of vitamin K (the absorption of which is bile-dependent). Concurrent obstruction of the pancreatic duct by a stone in the ampulla of Vater may be accompanied by increases in serum lipase and amylase levels.

Imaging modalities that may be useful include the following:

- Abdominal radiography (upright and supine) – Used primarily to exclude other causes of abdominal pain (eg, intestinal obstruction). Black pigment or mixed gallstones may contain sufficient calcium to appear radiopaque on plain films. The finding of air in the bile ducts on plain films may indicate development of a choledochoenteric fistula or ascending cholangitis with gas-forming organisms. Calcification in the gallbladder wall (the so-called porcelain gallbladder) is indicative of severe chronic cholecystitis. The main role of plain films in evaluating patients with suspected gallstone disease is to exclude other causes of acute abdominal pain, such as intestinal obstruction, visceral perforation, renal stones, or chronic calcific pancreatitis.
- Ultrasonography – The procedure of choice in suspected gallbladder or biliary disease. It is the most sensitive, specific, noninvasive, and inexpensive test for the detection of gallstones. It is highly sensitive and specific for gallstones greater than 2 mm. It is less so for microlithiasis or biliary sludge. Ultrasonography is very useful for diagnosing uncomplicated acute cholecystitis. The sonographic features of acute cholecystitis include gallbladder wall thickening (>5 mm), pericholecystic fluid, gallbladder distention (>5 cm), and a sonographic Murphy sign. The presence of multiple criteria increases its diagnostic accuracy.
- Endoscopic ultrasonography (EUS) – An accurate and relatively noninvasive means of identifying stones in the distal CBD

- Laparoscopic ultrasonography – Promising as a potential method for bile duct imaging during laparoscopic cholecystectomy
- Computed tomography (CT) – More expensive and less sensitive than ultrasonography for detecting gallbladder stones, but superior for demonstrating stones in the distal CBD
- Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) – Usually reserved for cases in which choledocholithiasis is suspected
- Scintigraphy – Highly accurate for the diagnosis of cystic duct obstruction
- Endoscopic retrograde cholangiopancreatography (ERCP) is usually performed in conjunction with endoscopic retrograde sphincterotomy and gallstone extraction.
- Percutaneous transhepatic cholangiography (PTC)

Differential Diagnoses

- Acute pancreatitis
- Appendicitis
- Bile duct strictures
- Bile duct tumors
- Cholecystitis
- Gallbladder cancer
- Pancreatic cancer
- Peptic ulcer disease

Treatment

The treatment of gallstones depends upon the stage of disease.

Medical treatments for gallstones, used alone or in combination, include the following:

- Oral bile salt therapy (ursodeoxycholic acid)
- Contact dissolution
- Extracorporeal shockwave lithotripsy

Treatment of asymptomatic gallstones

Surgical treatment of asymptomatic gallstones without medically complicating diseases is discouraged. The risk of complications arising from interventions is higher than the risk of symptomatic disease. Approximately 25% of patients with asymptomatic gallstones develop symptoms within 10 years.

However, cholecystectomy for asymptomatic gallstones may be indicated in the following patients:

- Patients with large gallstones, greater than 2 cm in diameter
- Patients with nonfunctional or calcified (porcelain) gallbladder observed on imaging studies and who are at high risk of gallbladder carcinoma
- Patients with spinal cord injuries or sensory neuropathies affecting the abdomen
- Patients with sickle cell anemia in whom the distinction between painful crisis and cholecystitis may be difficult

Patients with risk factors for complications of gallstones may be offered elective cholecystectomy, even if they have asymptomatic gallstones. These groups include persons with the following conditions and demographics:

- Cirrhosis
- Portal hypertension
- Children
- Transplant candidates
- Diabetes with minor symptoms

Patients with a calcified or porcelain gallbladder should consider elective cholecystectomy due to the possibly increased risk of carcinoma (25%). Refer to a surgeon for removal as an outpatient

procedure.

Medical dissolution of gallstones

In patients with established cholesterol gallstones, treatment with ursodeoxycholic acid at a dose of 8-10 mg/kg/d PO divided bid/tid may result in gradual gallstone dissolution. This intervention typically requires 6-18 months and is successful only with small, purely cholesterol stones. Patients remain at risk for gallstone complications until dissolution is completed. The recurrence rate is 50% within 5 years. Moreover, after discontinuation of treatment, most patients form new gallstones over the subsequent 5-10 years.

Treatment of patients with symptomatic gallstones

In patients with symptomatic gallstones, discuss the options for surgical intervention. Surgical interventions to be considered include the following:

- Cholecystectomy (open or laparoscopic)
- Cholecystostomy
- Endoscopic sphincterotomy

Prevention of gallstones

Ursodeoxycholic acid treatment can prevent gallstone formation. This has been demonstrated in the setting of rapid weight loss caused by very low-calorie diets or by bariatric surgery, which are associated with a high risk of new cholesterol gallstones (20-30% within 4 mo). Administration of ursodeoxycholic acid at a dose of 600 mg daily for 16 weeks reduces the incidence of gallstones by 80% in this setting.

Recommending dietary changes of decreased fat intake is prudent; this may decrease the incidence of biliary colic attacks. However, it has not been shown to cause dissolution of stones.

CHRONIC CHOLECYSTITIS

Cholecystitis is inflammation of the gallbladder that occurs most commonly because of an obstruction of the cystic duct by gallstones arising from the gallbladder (cholelithiasis). Uncomplicated cholecystitis has an excellent prognosis; the development of complications such as perforation or gangrene renders the prognosis less favorable. Ninety percent of cases involve stones in the gallbladder (ie, calculous cholecystitis), with the other 10% of cases representing acalculous cholecystitis.

Chronic inflammation of the gallbladder wall is almost always associated with the presence of gallstones and is thought to result from repeated bouts of subacute or acute cholecystitis or from persistent mechanical irritation of the gallbladder wall by gallstones. The presence of bacteria in the bile occurs in >25% of patients with chronic cholecystitis (CC). The presence of infected bile in a patient with CC undergoing elective cholecystectomy probably adds little to the operative risk. CC may be asymptomatic for years, may progress to symptomatic gallbladder disease or to acute cholecystitis, or may present with complications.

Epidemiology

An estimated 10-20% of Americans have gallstones, and as many as one third of these people develop acute cholecystitis. Cholecystectomy for either recurrent biliary colic or acute cholecystitis is the most common major surgical procedure performed by general surgeons. The incidence of cholecystitis increases with age. Gallstones are 2-3 times more frequent in females than in males, resulting in a higher incidence of calculous cholecystitis in females. Elevated progesterone levels during pregnancy may cause biliary stasis, resulting in higher rates of gallbladder disease in pregnant females. Acalculous cholecystitis is observed more often in elderly men.

Etiology

Main etiological factor for persistent inflammation of gallbladder is opportunistic pathogenic infections (E.coli, coccal flora), sometimes – other microbial causes (Proteus, Pseudomonas aeruginosa, etc.). Bacteria can get to gallbladder by contact path from the small intestine, or by hematogenic and lymphogenic path from any site of chronic inflammation.

Risk factors for calculous cholecystitis mirror those for cholelithiasis and include the following:

- Female sex
- Certain ethnic groups (people of Scandinavian descent, Pima Indians, and Hispanic populations)
- Obesity or rapid weight loss
- Drugs (especially hormonal therapy in women)
- Pregnancy
- Increasing age

Acalculous cholecystitis is related to conditions associated with biliary stasis, and include the following:

- Critical illness
- Major surgery or severe trauma/burns
- Sepsis
- Long-term total parenteral nutrition (TPN)
- Prolonged fasting

Other causes of acalculous cholecystitis include the following:

- Cardiac events, including myocardial infarction
- Sickle cell disease
- *Salmonella* infections
- Diabetes mellitus
- Patients with AIDS who have cytomegalovirus, cryptosporidiosis, or microsporidiosis

Patients who are immunocompromised are at an increased risk of developing cholecystitis from a number of different infectious sources. Idiopathic cases exist.

Pathophysiology

Development of CC is gradual. Entry of microbial flora against a background of GB hypotonia causes catarrhal inflammation of mucosa. Inflammation progresses to submucosa and muscular layer of GB, where it causes infiltration and activation of connective tissue. These processes lead to deformation of gallbladder and pericholecystitis development.

Calculous cholecystitis is caused by obstruction of the cystic duct, leading to distention of the gallbladder. As the gallbladder becomes distended, blood flow and lymphatic drainage are compromised, leading to mucosal ischemia and necrosis. Although the exact mechanism of acalculous cholecystitis is unclear, several theories exist. Injury may be the result of retained concentrated bile, an extremely noxious substance. In the presence of prolonged fasting, the gallbladder never receives a cholecystokinin (CCK) stimulus to empty; thus, the concentrated bile remains stagnant in the lumen.

Clinical presentation

Chronic cholecystitis may be asymptomatic for years. Dull pain in right upper quadrant (RUQ) and epigastrium and feeling of fullness may be present, can last for hours, increase after fatty, fried, spicy food, eggs, wine, beer. Pain radiates to right scapula or shoulder. Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. However, subfebrile body temperature may be present. Once episodes begin, they are likely to recur. Bitter taste in mouth sometimes is present in the morning. Nausea, belching, bloating are often reported.

Bowel movement disorders – alternation of constipations and diarrheas.

The absence of physical findings does not rule out the diagnosis of cholecystitis. Many patients present with diffuse epigastric pain without localization to the RUQ. Patients with chronic cholecystitis frequently do not have a palpable RUQ mass secondary to fibrosis involving the gallbladder.

Diagnosis

1. Ultrasonography.

Ultrasonographic criteria of inflammation in gallbladder:

- Thickness of wall of GB > 4 mm in the absence of liver and kidney pathology, and congestive heart failure;
- Increase of gallbladder size over 5 cm above the normal for the corresponding age;
- Presence of sonographic Murphy's sign;
- Presence of paracystic hypoechoic limbus (edema of gallbladder wall).

2. Cholecystography.

The following symptoms are characteristic for patients with CC:

- Absence of gallbladder shadow;
- Derangements of concentration ability and motility of gallbladder (delayed emptying);
- Deformation of gallbladder wall.

3. Duodenal intubation – can be conducted only if gallstones are absent! Helps to assess motor function of gallbladder. Provides 3 portions of bile for further studying of bile characteristics:

- Microscopy – signs of inflammation and lithogenicity of bile;
- Culture – determination of bacterial flora;
- Biochemical analysis – determination of cholesterol, bile acids, phospholipids in bile.

Treatment

Treatment of cholecystitis depends on the severity of the condition and the presence or absence of complications. Uncomplicated cases can often be treated on an outpatient basis. Antibiotics may be given to manage infection.

Treatment: phase of exacerbation.

Antibiotics. Indications for antibiotic therapy: presence of clinical and laboratory signs of inflammation, positive results of bile culture, cholangitis.

- Ciprofloxacin 500 mg 2/d per os, course 5 days
- Cefotaxime 1 g 2/d i/m
- Doxycycline 100 mg 2/d per os, course 5 days
- Amoxicillin 500 mg 3-4/d
- Tinidazole 4 pills per os once (if *Giardia* is a causative agent)

Symptomatic therapy:

1. Prokinetic agents – domperidone 10 mg or itoprid 50 mg 3/d 30 min prior to meals
2. Spasmolytics:
 - mebeverine 200 mg 2/d, course 3-4 weeks
 - drotaverine (No-Spa) 40 mg 3/d before meals
 - papaverine hydrochloride 2% - 2,0 i/m
3. Bile-expelling medications (cholagogues):
 - Preparations that stimulate cholepoietic function of liver (choleretics):
 - Preparations of bile acids: cholenzym, liobilum
 - Synthetic preparations: oxaphenamamide, cyclovalone
 - Preparations of herbal origin: strawflower extract, peppermint extract, corn stigmas
 - Preparations that improve secretion of bile by increasing of its aqueous component (hydrocholeretics) – mineral waters
 - Preparations that stimulate biliary excretion:

- Cholekinetics (increase tonus of GB and decrease tonus of bile ducts): xylite, sorbite, magnesium sulfate
 - Cholespasmolytics: anticholinergic drugs, aminophylline.
4. UDCA – 8-10 mg/kg/day (if microlites and/or stagnation of bile are present);
 5. Herbal hepatoprotectors with bile-expelling properties.
- Treatment:** phase of remission. Diet – meals 5-6 times a day, exclude fatty, fried, spicy, smoked food, pickles, alcohol. Phytotherapy. Mineral water. Physiotherapy. Exercise therapy.

FUNCTIONAL BILIARY DISORDERS

Biliary dyskinesia is a symptomatic functional disorder of the gallbladder whose precise etiology is unknown. It may be due to metabolic disorders that affect the motility of the GI tract, including the gallbladder, or to a primary alteration in the motility of the gallbladder itself.

Biliary dyskinesia presents with a *symptom complex* that is similar to those with biliary colic:

- Episodes of right upper quadrant pain
- Severe pain that limits activities of daily living
- Nausea associated with episodes of pain

The presumed mechanism for biliary pain is obstruction leading to distension and inflammation. This might result from incoordination between the gallbladder and either the cystic duct or the sphincter of Oddi due to increased resistance or tone. Central projections from visceral nociceptors to the thalamus and cortex might lead to a more excitable state with hyperalgesia (severe pain evoked by mildly painful stimuli). Persistent central excitability might then result in allodynia where innocuous stimuli produce pain.

Diagnosis

In order to diagnose biliary dyskinesia, the patient should have right upper quadrant pains similar to biliary colic but have a normal ultrasound examination of the gallbladder (no stones, sludge, microlithiasis, gallbladder wall thickening or common bile duct dilation). For patients who are suspected to have biliary dyskinesia, the **Rome III diagnostic criteria** for functional gallbladder disorders should be considered.

These include:

- Pain episodes that last longer than 30 minutes;
- Recurrent symptoms that occur at variable intervals;
- Pain that is severe enough to interrupt daily activity or lead to emergency room visits;
- Pain that builds up to a steady level;
- Pain that is not relieved by bowel movements, postural changes, or antacids;
- Exclusion of other structural diseases that could explain the symptoms;
- Other supportive criteria include: association of pain with nausea and vomiting, radiation of the pain to the infrascapular region, and pain that wakes the patient in the middle of the night;
- Normal liver enzymes, conjugated bilirubin, and amylase/lipase.

Screening tests

Laboratory

Tests of liver biochemistries and pancreatic enzymes must be normal.

The following tests are necessary to eliminate calculous biliary disease, which can produce similar symptoms.

Ultrasonography

Transabdominal ultrasonography of the upper abdomen is mandatory. The biliary tract and pancreas should be normal and gallstones or sludge absent. Ultrasonography readily detects stones equal to or greater than 3–5 mm in diameter or biliary sludge within the gall bladder, but it has a low sensitivity for smaller stones or biliary microcrystals. It also has a low yield for stones within the

common bile duct. Endoscopic ultrasonography seems to be more sensitive than traditional transabdominal ultrasonography in detecting microlithiasis (tiny stones <3 mm) and sludge within the biliary tract, but the recommendation for its inclusion in standard workups requires further evaluation.

Microscopic bile examination

This procedure is necessary to exclude microlithiasis as a cause. Gall bladder bile can be obtained directly at the time of endoscopic retrograde cholangiopancreatography (ERCP) or by aspiration from the duodenum following stimulation (e.g., cholecystikinin (CCK)-8 5 ng/kg i.v. over 10 minutes, or 50 ml MgSO₄ instilled into the duodenum). Two types of deposits may be evident: (1) cholesterol microcrystals, which are birefringent and rhomboid shaped, best visualized by polarizing microscopy. Their presence provides a high diagnostic accuracy for microlithiasis; and (2) bilirubinate granules, which appear as red-brown deposits under conventional light microscopy.

Endoscopy

In the presence of normal laboratory and ultrasonographic findings, endoscopy is usually indicated to exclude upper gastrointestinal diseases.

Tests for gall bladder dysfunction

CCK–cholescintigraphy assessment of gall bladder emptying

This study continuously monitors the hepatic excretion of a radiopharmaceutical into the gall bladder and duodenum, using computer assistance to quantitate changes in radioactivity over the gall bladder. Filling of the gall bladder with radionuclide indicates patency of the cystic duct. Gall bladder emptying is expressed as the gall bladder ejection fraction, the percentage decrease in net gall bladder counts following CCK infusion (CCK-8 slowly infused at 20 ng/kg over 30 minutes). Reduced emptying, which defines gall bladder dysfunction, can arise from either depressed gall bladder contraction or increased resistance such as elevated tone in the sphincter Oddi. Furthermore, several other conditions that do not necessarily present with biliary colic can be associated with reduced gall bladder emptying. These range from intrinsic gall bladder disease (stones, cholecystitis) to neural and metabolic disorders, drugs, and even the irritable bowel syndrome. Although biliary-type pain is rarely elicited, the test appears to be a marker of this biliary disorder, based on evidence of the beneficial effect of cholecystectomy.

Transabdominal ultrasonography

This test measures gall bladder volume, which if followed serially after a stimulus (meal or CCK), reflects emptying. The technique is operator dependent and the results may not be reproducible in different centers. Ultrasonographic assessment of gall bladder emptying is currently not the standard for gall bladder dysfunction.

Pain provocation test

Stimulation tests with CCK to duplicate biliary pain have been used historically as a diagnostic investigation. Such tests have low sensitivity and specificity in selecting patients with gall bladder dysfunction who respond to therapy. This may relate to problems in the subjective assessment of pain and the use of bolus injections of CCK, which can induce intestinal contractions.

Diagnostic workup

Biliary tract symptoms should be evaluated by liver biochemistry, pancreatic enzymes, and ultrasound examination of the abdomen. As a general recommendation we suggest that invasive investigations should be withheld in those patients in whom episodes are infrequent and not accompanied by increased liver function tests.

- If no abnormal findings are detected, CCK–cholescintigraphy should be used to assess gall bladder emptying. Abnormal gall bladder emptying (<40% ejection) indicates gall bladder dysfunction.
- If there is no obvious cause for impaired emptying, cholecystectomy is appropriate treatment.
- If gall bladder emptying is normal, bile for microscopic examination to detect cholesterol microcrystals and bilirubinate can be obtained by duodenal drainage, at the time of gastrointestinal endoscopy or during ERCP. Magnetic resonance cholangiography or endoscopic ultrasound, where available, can be performed to detect lithiasis.

- If gall bladder emptying is normal, ERCP should be considered. In the absence of common bile duct stones or other abnormalities, SO manometry should be considered if clinically indicated. Evidence of SO dysfunction is an indication for treatment, which may include sphincterotomy.

Treatment strategies

Medical therapy remains theoretical. It might take the form of:

1. Altering gall bladder motor function (use of motility agents which enhance gall bladder contractility or ursodeoxycholic acid which worsens motility yet lessens the likelihood of biliary pain);
2. Reducing visceral hyperalgesia or inflammation (non-steroidal anti-inflammatory drugs) ;
3. Cholecystectomy. Laparoscopic cholecystectomy retains a role in the treatment of gall bladder dysfunction, although favorable outcomes may deteriorate with time.

Control of initial level of knowledge:

1. The main components of bile typically DON'T include:

- A. Water
- B. Bile salts
- C. Cholesterol
- D. Phospholipids
- E. Organic matrix

2. The incidence of gallstones in the population of developed countries is:

- A. 5-10%
- B. 10-15%
- C. 15-20%
- D. 20-25%
- E. 40-60%

3. Cholesterol stones occur in patients:

- A. with cirrhosis
- B. with bile supersaturated with cholesterol
- C. elderlies
- D. with infection of biliary tract
- E. with pancreatitis

4. Black pigment stones occur in patients:

- A. with hemolytic disease
- B. with hypertriglyceridemia
- C. after surgical interventions on biliary tract
- D. with the accumulation of insoluble bilirubin in the bile
- E. with bleeding

5. Brown pigment stones occur in patients with:

- A. bile supersaturated with cholesterol
- B. the accumulation of insoluble bilirubin in the bile
- C. hemolytic diseases
- D. hypertriglyceridemia
- E. infection of biliary tract

6. List the etiological factors for chronic cholecystitis:

- A. obesity;
- B. impaired lipid metabolism;
- C. gallbladder dyskinesia;
- D. dysfunction of the autonomic nervous system;
- E. everything mentioned above.

7. Which of the etiologic factors is the most common for the formation of chronic cholecystitis?

- A. bacteria;
- B. virus;
- C. lamblia;
- D. aseptic;
- E. impaired lipid metabolism.

8. What are the clinical symptoms typical for cholecystitis?

- A. pain syndrome;
- B. premenstrual tension;
- C. dyspeptic;
- D. solar;
- E. everything mentioned above

9. Which of the following is NOT a specific cause of biliary colic?

- A. hormone therapy;
- B. family history;
- C. intake of fatty foods;
- D. Caucasian ethnicity;

10. Which of the following is recommended for patients with large symptomatic gallstones?

- A. cholecystectomy;
- B. expectant management;
- C. stone fragmentation using extracorporeal shock wave lithotripsy;
- D. stone dissolution using UDCA;
- E. topical dissolution therapy.

Control of final level of knowledge:

1. The 'solar syndrome' in chronic cholecystitis is:

- A. pain in the right upper quadrant;
- B. pain in the left upper quadrant;
- C. cardialgia;
- D. pain in right shoulder;
- E. pain under xiphoid process.

2. Which of the following symptoms does the dyspeptic syndrome in chronic cholecystitis include?

- A. heartburn, nausea;
- B. bitter taste in mouth;
- C. single vomiting, bringing relief;
- D. repeated vomiting, no relief;
- E. excessive stool.

3. What causes steady dull pain in the right upper quadrant in chronic cholecystitis?

- A. gallbladder dyskinesia, hypertonic type;

- B. gallbladder dyskinesia, hypotonic type;
- C. presence of gallstones;
- D. concomitant chronic pancreatitis;
- E. accompanying gastroduodenitis.

4. What is the character of pain in gallbladder dyskinesia, hypertonic type?

- A. steady, dull;
- B. spastic;
- C. burning
- D. mild aching;
- E. dull, oppressive.

5. What stimulant is used for cholescintigraphy assessment of gall bladder emptying?

- A. histamine;
- B. cholecystokinin;
- C. magnesium sulfate;
- D. aminophylline;
- E. caffeine.

6. In addition to older age, female sex, and obesity, which of the following is a risk factor for gallstones?

- A. rapid weight loss
- B. high fiber diet;
- C. low fat diet;
- D. pancreatitis;

7. What factors contribute to formation of cholesterol stones in the gall bladder?

- A. hereditary predisposition;
- B. impaired lipid metabolism
- C. obesity;
- D. chronic cholecystitis;
- E. everything listed above

8. In a patient with suspected gallstones, which of the following is the most reliable diagnostic tool?

- A. plain Xray of abdomen
- B. ultrasonography
- C. elimination diet
- D. lipid profile

9. The cause of obstructive jaundice in GD is one of the following:

- A. stone blocking the neck area of gallbladder
- B. cystic duct blockage
- C. blockage of the common bile duct
- D. pancreatic duct blockage
- E. hepatic duct blockage

10. Most of the gallstones comprise of the following:

- A. calcium carbonate
- B. calcium stearate
- C. bile
- D. cholesterol
- E. mucus

Case-based questions.

1. The patient of 44 years old complains of periodic pain in epigastric area that radiates to the right shoulder; periodic jaundice with fever, bitter taste in mouth. These complaints typically occur after overeating. Objective examination: the patient is overweight, the scleras are icteric, local tenderness in the right upper quadrant, positive Ker's and Ortner's symptoms. The content of direct bilirubin in blood is increased. What is the most likely diagnosis?

- A. Dyskinesia of the gall bladder;
- B. Gallstone disease;
- C. Chronic pancreatitis;
- D. Peptic ulcer;
- E. Hiatal hernia

2. A woman of 58 years old was delivered to the emergency room with intense pain in the upper abdomen that occurred suddenly after eating french fries. Pain was accompanied by nausea and vomiting. Pain lasted about an hour before the arrival to the emergency room and passed away without assistance. Patients has previous history of cholecystitis. Objective examination: pulse rate - 92 for 1 min; moderate to intense pain upon palpation in the right upper quadrant. What is the most likely cause of abdominal pain?

- A. Myocardial infarction;
- B. Acute cholangitis;
- C. Acute pancreatitis;
- D. Biliary colic;
- E. Peptic ulcer perforation

3. Male, 55, complains of pain in the right upper quadrant radiating to the right shoulder, related to the intake of fatty foods; nausea, poor sleep. Patients has had previous history of chronic cholecystitis during past 12 years. Objective examination: moderate flatulence, pain at the point of gallbladder projection, positive Ortner's symptom. Body temperature - 37.7° C. CBC: L - $12.7 \times 10^9 / L$, neutrophils - 16%, ESR - 27 mm / h. The microscopic examination of second portion of duodenal contents revealed a lot of mucus, epithelial cells, and leukocytes. What antibiotic would be the best choice for this patient?

- A. Ampicillin;
- B. Penicillin;
- C. Nitroxoline;
- D. Rystomycin;
- E. Chloramphenicol

4. Female, 29 years, complains of constant nagging pain, feeling of heaviness in the right upper quadrant, sometimes sharp pain radiating to the back, nausea, bitter taste in the mouth, heartburn, which tends to worsen in the late afternoon. She is 28 weeks pregnant. Objective examination: tenderness during palpation in epigastric area and right upper quadrant, especially in projection of gallbladder. Previous ultrasonography detected opacities in gallbladder lumen. What is the most likely diagnosis?

- A. Acute pancreatitis;
- B. Gallstone disease;
- C. Acute gastritis;
- D. Dyskinesia of biliary tract;
- E. Peptic ulcer

5. Female, 46, complains of a dull pain in the right upper quadrant, fatigue, skin itch, recurrent fever during 3 years. Paroxysmal pain is sometimes accompanied by fever and increased itching.

Objective examination: yellow scleras, body temperature - 37.5° C, tenderness in the right upper quadrant, the liver extends over the edge of costal arch by 3 cm, and it is dense and painful. The spleen is not palpable. CBC: Hb - 121 g / L, L - 11×10^9 / L, neutrophils - 14%, ESR - 30 mm / h. What is the most likely diagnosis?

- A. Hemolytic anemia;
- B. Chronic cholecystitis;
- C. Chronic cholangitis;
- D. Chronic hepatitis;
- E. Cirrhosis

6. The patient, 34 years old, complains of aching pain in the right upper quadrant, which increases after eating fatty and fried foods, bitter taste in mouth. He has been ill for 9 years. Objective examination: overweight, normal skin color, moderate pain in the right upper quadrant, tenderness upon palpation in the right upper quadrant. Liver is not enlarged. Results of duodenal intubation: 85 ml of bile were obtained from the gall bladder during 55 minutes, the microscopic examination of bile revealed leukocytes. What is the most likely diagnosis?

- A. Chronic cholecystitis with gallbladder dyskinesia;
- B. Gallstone disease;
- C. Gallbladder dyskinesia;
- D. Chronic cholecystitis;
- E. Cancer of the gallbladder

7. The patient, 35 years old, woke up at night due to the sudden, sharp pain in the right upper quadrant that irradiated to the right scapula. Pain was accompanied by nausea and repeated vomiting. Kehr's and Murphy's symptoms are positive. Which of the following is the most effective drug to stop pain attack?

- A. Benzocaine;
- B. Morphine;
- C. Atropine.;
- D. Metoclopramide;
- E. Promedol

8. Male, 48, has visited doctor due to complaints of paroxysmal pain in the right upper quadrant and nausea. On the next day jaundice has appeared. Such attacks of recurrent jaundice repeated twice during 1.5 years. Objective examination: yellow scleras, dry tongue, meteorism, tenderness upon palpation in the RUQ, positive Ortner's symptom. CBC: L 10.0×10^9 / L, neutrophils - 16%, ESR - 25 mm / h. What additional research would be the most informative for making the diagnosis?

- A. Laparoscopy
- B. Abdominal ultrasound.
- C. Duodenal intubation
- D. Oral cholecystography
- E. Plain abdominal X-ray

9. Woman, 34 years old, was delivered to the hospital with paroxysmal pain in the right upper quadrant, which developed after a stressful situation. These repeated attacks have continued throughout the year. Objective examination: satisfactory general condition, abdomen is soft, slightly painful in the region of the gallbladder. Examination of lungs and heart revealed no pathologic signs. Abdominal ultrasound and CBC data were normal. The preliminary diagnosis is gallbladder dyskinesia. Duodenal intubation is planned. What changes in the duodenal intubation report can confirm the preliminary diagnosis?

- A. Reduced Phase III;
- B. Reduced time of the second phase;

- C. Extended Phase II;
- D. Increase volume of bile in the portion III;
- E. Incomplete emptying of the gallbladder

10. A 60-year-old man undergoes a CT scan to evaluate his abdominal aorta. The images show a normal aorta, but his gallbladder contains several stones, and intramural calcification of the gallbladder wall also is noted. No other abnormal findings are seen. The patient has not had any symptoms and has normal liver chemistries. What is the most appropriate therapy for this patient?

- A. Cholecystectomy
- B. Cholecystojejunostomy
- C. Endoscopic retrograde cholangiopancreatography to evaluate the biliary tree
- D. Endoscopic ultrasound of the gallbladder and biliary tree
- E. Observation

The correct answers to test questions:

Initial level of knowledge:

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

The final level of knowledge:

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

Case-based questions:

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

Control questions:

1. Provide the definition of GD, CC, and biliary dyskinesia.
2. The main clinical syndromes of biliary tract diseases.
3. Physical findings upon examination of the patient with GD.
4. Diagnostic criteria of chronic cholecystitis.
5. The types of biliary dyskinesias.
6. Pathogenesis of GD.
7. Diagnostic workup in gallbladder dyskinesia.
8. The complications of GD and CC.
9. List the possible causes for CC, GD and peculiarities of the disease, depending on the etiological factor.
10. Describe the pathogenesis of CC.
11. Principles of treatment of GD, CC and biliary dyskinesias.
12. Pharmacological therapy of GD and CC.
13. Indications for surgical treatment of GD, CC and biliary dyskinesias.
14. Prevention of GD and CC

Practical tasks:

1. To perform physical examination of patient with biliary tract diseases.
2. To interpret the received data of laboratory tests.
3. To interpret the received data of instrumental tests.
4. To write recipes for the treatment of GD.

Clinical examination of the patient

Name of the patient _____

Age _____ profession _____

Complaints _____

Anamnesis morbi

Anamnesis vitae

The results of physical examination of the patient:

Preliminary diagnosis:

The results of additional research methods:

Substantiation of clinical diagnosis:

Clinical diagnosis:

Main

diagnosis _____

Concomitant pathology

Complications

Treatment:

1. _____
2. Diet _____
3. _____
4. _____
5. _____

Materials for self-preparation:

1. Davidson's "Principles and Practice of Medicine" 21st edition, Alimentary tract and pancreatic disease, p. 835-919.
2. Current Medical Diagnosis and Treatment, Gastrointestinal disorders, 2014, p. 564-662
3. Harrison's, Principles of Internal Medicine, 19th edition, Gastroenterology and Hepatology, p.257-398
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6. Functional Hepatobiliary Disease: Chronic Acalculous Gallbladder and Chronic Acalculous Biliary Disease. Ziessman, H.A. Semin Nucl Med. 2006; 36:119-132.
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9. Functional Gallbladder and Sphincter of Oddi Disorders. Behar et el. Gastroenterology. 2006 Apr;130 (5):1498-509.
10. General Surgery: Principles and International Practice. Springer Science & Business Media, Nov 12, 2008 - Medical - 2011 pages.
11. Functional gallbladder disorder: an increasingly common diagnosis. David I.C. Lakeland Regional Family Health Center, Lakeland, Florida. Am Fam Physician. 2014 May 15;89 (10):779-784.
12. Management of Gallstones and Their Complications. Aijaz A., Ramsey C. C., Emmet B. K., Stanford University School of Medicine, Stanford, California. Am Fam Physician. 2000 Mar 15;61(6):1673-1680.
13. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. *Lancet*. 2006 Jul 15. 368(9531):230-9.

Інформаційні ресурси

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З доповненнями (змiнами) _____

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