

Ministry of Healthcare of Ukraine

**Poltava State Medical University**

Approved

at the meeting of Internal Medicine №1

Department “ \_\_\_\_ ” \_\_\_\_\_

Protocol № \_\_\_\_ from \_\_\_\_\_

The Head of the Department

Associate Professor Maslova H.S.

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**Methodical guidelines**

**for students’ self-studying to prepare**

**for practical (seminar) classes and on the lessons**

Academic discipline	Internal medicine
Module №	1
Topic of the lesson	Chronic cholecystitis and functional biliary disorders. Cholelithiasis.
Course	IV
Faculty	of foreign students training

**1. Relevance of the topic: Chronic cholecystitis** is a prolonged, subacute condition caused by the mechanical or functional dysfunction of the emptying of the gallbladder. It presents with chronic symptomatology that can be accompanied by acute exacerbations of more pronounced symptoms (acute biliary colic), or it can progress to a more severe form of cholecystitis requiring urgent intervention (acute cholecystitis). There are classic signs and symptoms associated with this disease as well as prevalences in certain patient populations. The two forms of chronic cholecystitis are with cholelithiasis (with gallstones), and acalculous (without gallstones).

**Functional biliary disorders** are controversial topics. They have gone by a variety of names, including acalculous biliary pain, biliary dyskinesia, dysmotility.

**2. Certain aims:**

- To be able to assess the typical clinical picture of chronic calculous and acalculous cholecystitis and functional biliary disorders, to determine tactics of treatment and prophylaxis;
- To select the information indicating the presence of chronic calculous and acalculous cholecystitis and functional biliary disorders in a patient from the data history;
- To create a scheme of diagnostic search;
- To identify the signs of chronic calculous and acalculous cholecystitis and functional biliary disorders in an objective study of the patient (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 of chronic calculous and acalculous cholecystitis and functional biliary disorders according to classification;
- To conduct differential diagnostics of diseases with the similar clinical picture;
- 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 required to study the topic (interdisciplinary integration).**

Names of previous disciplines	Obtained skills
1. Anatomy 2. Histology 3. Physiology 4. Pathology 5. Radiology 6. Propaedeutic internal medicine 7. Pharmacology	To describe the structure of the gastrointestinal tract, blood supply and innervation in health and disease; to establish the preliminary diagnosis, to use additional methods of examination and interpret their data to make final diagnosis; to manage the patient with chronic cholecystitis; to classify cholecystitis, biliary dyskinesia; drugs for their treatment; to identify markers of gastrointestinal tract function and to know their normal values; to draw a scheme of patient's follow-up; to compare cholecystitis with other diseases with the same symptoms; to demonstrate practical skills during physical examination of the patient, analyzing the clinical and laboratory results.

#### **4. Tasks for self-studying to prepare for the lesson and on the lesson.**

4.1. List of main terms, parameters, characteristics that should be learnt by student during preparation for the classes:

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 disease of the hepatobiliary system caused by the metabolic imbalance of cholesterol and (or) bilirubin in combination with other factors that leads to the formation of stones in the gallbladder and (rarely) bile ducts.
Functional biliary disorders	symptom complexes not explained by a clearly identified mechanism or by a structural alteration.
Cholekinetics	are substances which increases 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.

#### **4.2. Theoretical questions for the lesson:**

1. Give the definitions of chronic calculous and acalculous cholecystitis and functional biliary disorders.
2. Specify the risk factors for chronic calculous and acalculous cholecystitis and functional biliary disorders.

3. The pathophysiological mechanisms of chronic calculous and acalculous cholecystitis and functional biliary disorders.
4. Diagnostic criteria of chronic calculous and acalculous cholecystitis and functional biliary disorders.
5. What are the instrumental characteristics of chronic calculous and acalculous cholecystitis and functional biliary disorders?
6. Modern classification of chronic calculous and acalculous cholecystitis and functional biliary disorders.
7. Specify the principles and features of chronic calculous and acalculous cholecystitis and functional biliary disorders pharmacotherapy according to modern recommendations.
8. What lifestyle modifications should be recommended for patients with chronic calculous and acalculous cholecystitis and functional biliary disorders?

#### **4.3. Practical work (tasks), performed on the lesson:**

1. Interpret changes in general blood test in case of chronic calculous and acalculous cholecystitis and functional biliary disorders.
2. Interpret data of biochemical blood tests in case of chronic calculous and acalculous cholecystitis and functional biliary disorders.
3. Perform survey and physical examination of the patient and make preliminary diagnosis.
4. Manage the patient with suspected of chronic calculous and acalculous cholecystitis and functional biliary disorders, prescribe relevant laboratory and instrumental investigations and further treatment.
5. Interpret data of ultrasounds examination of chronic calculous and acalculous cholecystitis and functional biliary disorders.

#### **Topic Content:**

### **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). Cholesterolosis 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 these gastrointestinal 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 E2 (PGE2).

**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 unmasks 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 hilumduodenum 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 risks 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.

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

### **A. Tests and situational tasks for self-control:**

1. 50 years old patient is suffering from attacks of pain in the right subcostum for a year, which arise up mainly after rich meals. Last week attacks repeated daily, became more painful. On the 3rd day of hospital treatment yellowness of scleras and skin, light feces and dark urine appeared. Blood test: Hb - 128 g/l, retic - 2%, neutrophile leukocytosis -  $13,1 \times 10^9/l$ , blood sedimentation - 28 mm/h. What is the most credible reason of icterus?

- A) Chronic pancreatitis
- B) Cholecystolithiasis
- C) Chronic cholestatic hepatitis
- D) Hemolytic anemia
- E) Acute viral hepatitis

2. 28 years old woman, who was conducted laparoscopic cholecystectomy 1,5 year ago complains of pain in the right subcostum, acholic feces, darkening of urine. What method is necessary to be used for clarification of the diagnosis?

- A) Ultrasonic research
- B) Retrograde cholangiography
- C) Scintigraphy of liver
- D) Termography of trunk
- E) Esophagogastroduodenoscopy

3. 41 years old woman has been suffering from chronic cholecystitis during 8 years. She has complaints on permanent monotonous pain, heavy feeling in the right subcostum, bitter taste in mouth in the morning, constipations. Upon the palpation of abdomen painfulness in the point of gallbladder projection was detected. The volume of gall-bladder after cholagogic breakfast decreased just on 15% (according to US research). What preparations are the most appropriate in this situation?

- A) Cholaretics

- B) Peripheral M-cholinolytics
- C) Myothropic spasmolytics
- D) Non-narcotic analgetics
- E) Cholekinetics

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 reccurent 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 -  $36,8 \text{ mkmol/l}$ , direct -  $26,4 \text{ mkmol/l}$ , indirect -  $10,4 \text{ mkmol/l}$ . 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. Choleretic
- B. Ursofalc
- C. Cholekinetic
- D. Spasmolytic
- E. Cytostatic preparations

11. 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?

12. Patient O., 30 years old, complains of attacks of brief pain in the right subcostum. There is a connection with violation of diet, nervous overload. Painful points and areas of skin hyperesthesia were not found. Data of fractional duodenal tubage: lengthening of second and third phase time, reducing of selection time of vesical bile, at saving of vesical bile volume. What is the probable diagnosis? What groups of preparations should be prescribed for treatment?

Answers: 1-B, 2-B, 3-E, 4-E, 5-A, 6-A, 7-A, 8-A, 9-A, 10-B. 11. Chronic cholecystitis with hypomotoric dyskinesia. US, ERCPG, bacteriological research of bile. 12. Hyperkinetic dyskinesia of gall bladder. Cholekinetics, antispasmodics.

### **Recommended literature**

#### **I. Main:**

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.
3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у 3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічна дія ліків – Side Effects of Medications: навчальний посібник у 2 т. / заг. ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:

6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

## **II. Additional literature:**

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. -Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook fur medical students / Ye. Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143 .
7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook

9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).