МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ПОЛИКЛИНИЧЕСКОЙ ТЕРАПИИ

Е. С. Алексеева, В. В. Дрощенко

ЖЕЛЧНОКАМЕННАЯ БОЛЕЗНЬ, ХРОНИЧЕСКИЙ ХОЛЕЦИСТИТ И ФУНКЦИОНАЛЬНЫЕ НАРУШЕНИЯ ЖЕЛЧЕВЫВОДЯЩИХ ПУТЕЙ В АМБУЛАТОРНОЙ ПРАКТИКЕ

GALLSTONE DISEASE, CHRONIC CHOLECYSTITIS AND FUNCTIONAL BILIARY DISORDERS IN OUTPATIENT PRACTICE

Учебно-методическое пособие

Минск БГМУ 2024

УДК [616.366-003.7+616.361-002]-039.57(075.8)-054.6
ББК 54.13я73
А46

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 29.06.2022 г., протокол № 6

Рецензенты: канд. мед. наук, доц. 2-й каф. внутренних болезней О. А. Паторская; каф. пропедевтики внутренних болезней

Алексеева, Е. С.

А46 Желчнокаменная болезнь, хронический холецистит и функциональные нарушения желчевыводящих путей в амбулаторной практике = Gallstone disease, chronic cholecystitis and functional biliary disorders in outpatient practice : учебно-методическое пособие / Е. С. Алексеева, В. В. Дрощенко. – Минск : БГМУ, 2024. – 40 с.

ISBN 978-985-21-1506-3.

Представлены сведения о патофизиологии, эпидемиологии, клинических проявлениях, диагностике патологии желчевыводящих путей, рассмотрены вопросы дифференциальной диагностики и лечения.

Предназначено для студентов 4–6-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

УДК [616.366-003.7+616.361-002]-039.57(075.8)-054.6
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ISBN 978-985-21-1506-3

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ABBREVIATIONS

CBC — complete blood count
CBD — the common bile duct
CC — chronic cholecystitis
GD — gallstone disease
CT — computed tomography
ERCP — endoscopic retrograde cholangio-pancreatography
EUS — endoscopic ultrasound
ICU — intensive care unit
FBSD — functional biliary sphincter disorder
MRI — magnetic resonance imaging
NAFLD — nonalcoholic fatty liver disease
PTC — percutaneous transhepatic cholangiography
RUQ — right upper quadrant
SOD — sphincter of oddi dysfunction
UDCA — ursodeoxycholic acid

BILIARY SYSTEM ANATOMY AND FUNCTIONS

The knowledge of relevant anatomy is of vital importance for understanding and managing biliary disorders. The basic anatomy review is illustrated in fig. 1–3. It may be a good idea to return to this chapter from time to time while reading.

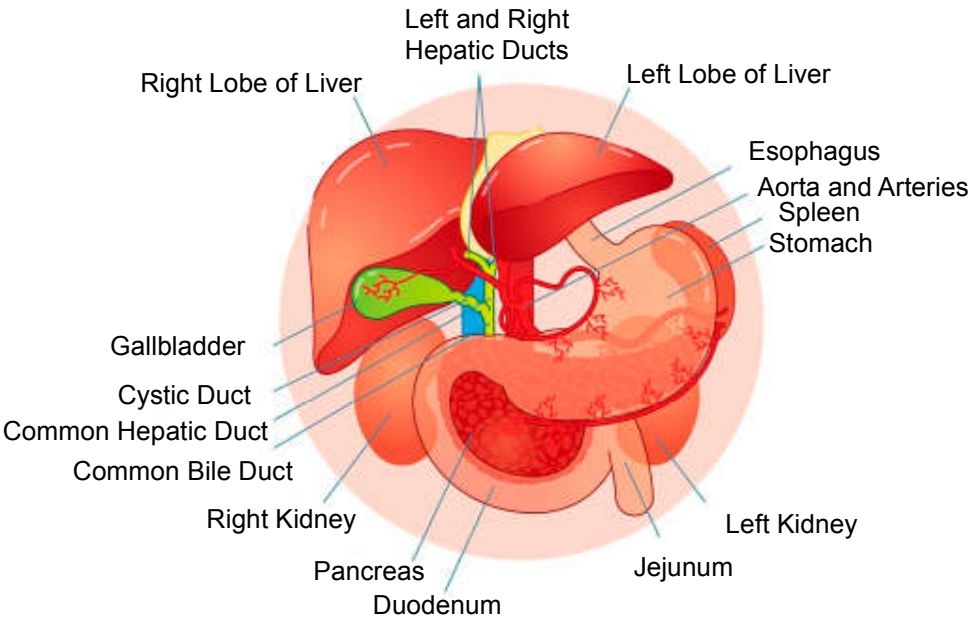


Fig. 1. Biliary tract' anatomy (https://en.wikipedia.org/wiki/Biliary_tract)

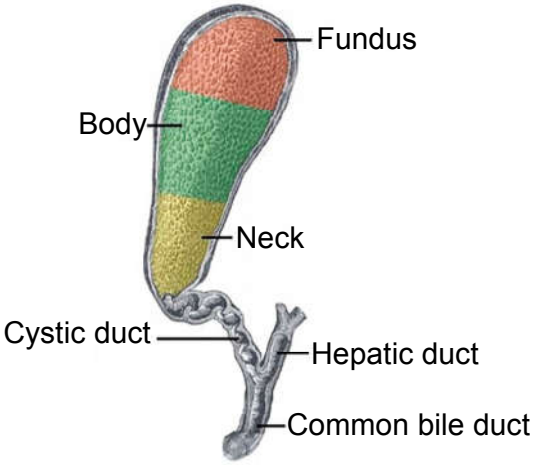


Fig. 2. The parts of the gallbladder and proximal biliary tree (https://teachmeanatomy.info/abdomen/viscera/gallbladder)

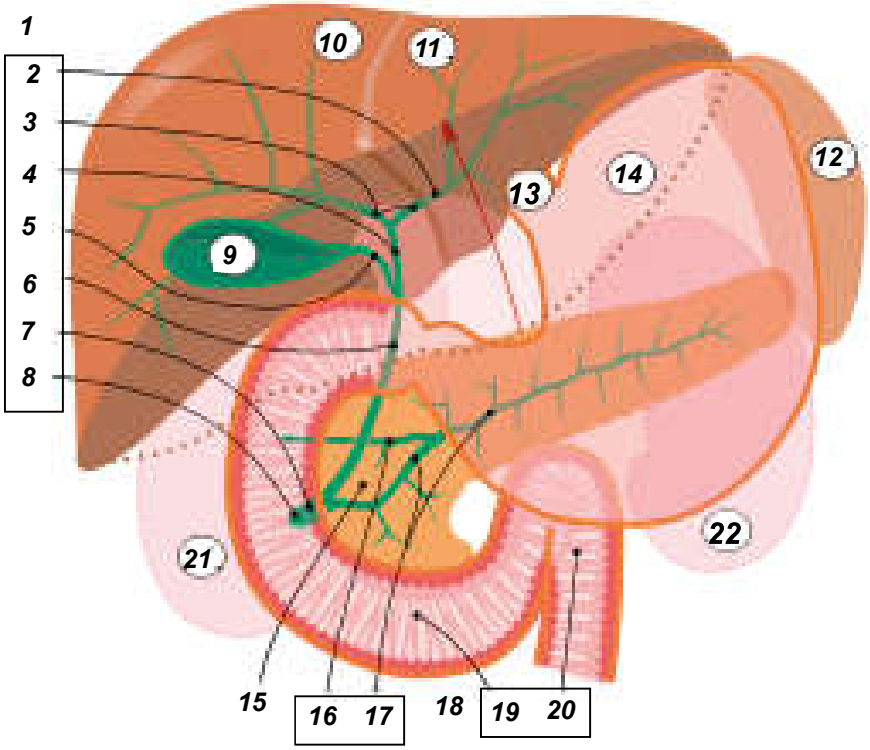


Fig. 3. Hepatobiliary tract' structure (Standring S., Borley N. R., eds. (2008). Gray's anatomy : the anatomical basis of clinical practice. Brown J. L., Moore L. A. London : Churchill Livingstone):

1 — bile ducts; *2* — intrahepatic bile ducts; *3* — left and right hepatic ducts; *4* — common hepatic duct; *5* — cystic duct; *6* — common bile duct; *7* — ampulla of vater; *8* — major duodenal papilla; *9* — gallbladder; *10–11* — right and left lobes of liver; *12* — spleen; *13* — esophagus; *14* — stomach; *15* — pancreas; *16* — accessory pancreatic duct; *17* — pancreatic duct; *18* — small intestine; *19* — duodenum; *20* — jejunum; *21–22* — right and left kidneys

The biliary system consists of the organs and ducts (bile ducts, gallbladder, and associated structures) that are involved in the production and transportation of bile.

To fully understand how the biliary system works, it's important to know the definition of some related medical terms, including the following.

Duodenum: it is the first of three sections of the small intestine, and receives food from the stomach and digestive juices from the liver, gallbladder, and pancreas via the biliary tract. This is the part of the small intestine that is primarily involved in breaking down food so that nutrients can later be absorbed in the jejunum (middle section of the small intestine).

Liver: a large glandular organ performs many vital metabolic functions, such as the digestion of fats to make energy in the body. The liver cells make bile.

Bile: a thick, greenish-brown substance made in the liver and stored in the gallbladder, bile consists of water, bile acids, cholesterol, phospholipids, bile pigments (such as bilirubin), and electrolytes. It is important in enabling the body to digest and absorb fats and fat-soluble vitamins, such as vitamins D and K.

Bile duct: this is a small, hollow tube that functions to transport bile. The biliary system is composed of a system of these ducts, which flow from the liver to the gallbladder for storage and then into the small intestine (duodenum).

Gallbladder: a pear-shaped organ located in front of the duodenum, just underneath the liver, the gallbladder's main function is to store bile. It is connected with the cystic duct.

Pancreas: a large gland located behind the stomach, the pancreas secretes pancreatic enzymes (such as lipase, which breaks down fats) into the biliary system via the pancreatic duct.

Gallstone: abnormal, small, hard masses comprised of bile pigments, cholesterol, and calcium salts, gallstones can cause a blockage of bile ducts, a condition called cholestasis.

Through the system of ducts and other structures of the biliary system, bile travels in a controlled manner.

From the liver, where bile is made in the liver cells, next it flows into a system of ducts located inside and outside of the liver. These ducts function to collect the bile. Once collected, the bile travels to the right and left hepatic ducts.

From the right and left hepatic ducts, bile then flows into the common hepatic duct.

The common hepatic duct joins the cystic duct, where the bile then flows.

The cystic duct is connected with the gallbladder. Bile flows from the cystic duct into the common bile duct.

The common bile duct (CBD) is located where the common hepatic duct and the cystic duct join. The CBD runs from the liver to the duodenum, where bile is excreted through a muscular opening called the sphincter of Oddi.

The common bile duct passes through the pancreas before it empties into the duodenum. The lower portion of the CBD joins the pancreatic duct before entering the duodenum. It is where pancreatic juices (containing digestive enzymes) enter the biliary system.

The sphincter of Oddi relaxes to allow bile to enter the duodenum. Once the bile enters the duodenum, it begins to break down ingested fats. Only half of the bile ends up in the duodenum, while the other half travels into the gallbladder.

The gallbladder receives half of the bile that flows through the common bile duct, where it is stored in the gallbladder for future use.

Once bile is stored in the gallbladder, it isn't released until a large meal is eaten and a hormone named cholecystokinin gets secreted. This hormone stimulates the release of bile, which travels to the duodenum through the cystic duct and into the common bile duct to begin the process of breaking down fats.

Aberrant ducts are a common variation from the normal anatomy that comprises the biliary system. Aberrant ducts are not anatomically structured the way they should be. For example, the ducts may abnormally join the wrong ducts, so that bile does not flow properly.

In fact, according to a study published in Liver and Biliary Tract Surgery, «50 % of patients presenting with gallbladder stones or common bile duct stones show a significant variation from what is generally considered as the expected normal pattern» [1].

There are three important functions of the biliary system:

1. Draining the waste products from the liver (into the duodenum)
2. Secreting bile in a controlled-release manner
3. Transporting bile and pancreatic juices to help break down food in the small intestine.

BILE ACID BIOLOGY AND PHYSIOLOGY

Bile acid synthesis is an important pathway for the catabolism of cholesterol and is tightly regulated by a complex of an integrated network of mechanisms but at the same moment can be highly toxic if accumulated in high concentrations in the liver and other tissues.

Recent research has revealed that bile acids are signaling molecules that activate nuclear receptors and membrane G protein-coupled bile acid receptors to regulate not only the classic bile acid synthesis pathway but also the alternative bile acid synthesis pathways to maintain lipid, glucose, and energy metabolism in the liver, intestine, and adipose tissue.

Alteration of bile acid homeostasis affects hepatic metabolic homeostasis, causes inflammation, and contributes to the pathogenesis of metabolic diseases such

as nonalcoholic fatty liver disease (NAFLD), diabetes, obesity, and inflammatory bowel diseases.

The gut-to-liver axis and circadian rhythms in bile acid metabolism. Bile acid synthesis in the liver is controlled in part by circadian expression of CYP7A1 expression. Bile acids control the gut microbiota population, and gut bacteria regulate bile acid metabolism, bile acid composition, and enterohepatic circulation of bile acids. Sleep disruption, high-fat diet, alcohol, and drugs alter the central clock in the hypothalamic suprachiasmatic nucleus of the brain cause the desynchronization of the peripheral clocks in the liver and intestine.

Disruption of circadian rhythms alters bile acid homeostasis, causes liver and intestine inflammation and dysbiosis, and contributes to cholestatic liver injury, NAFLD, diabetes, and inflammatory bowel diseases. Bile acids are required for the absorption of fats, steroids, and lipid-soluble vitamins in the intestine for metabolism in the liver and are signaling molecules that activate nuclear and membrane bile acid receptors to modulate hepatic lipid, glucose, and energy metabolism.

In the liver, the conversion of cholesterol to bile acids is the major pathway for the catabolism of cholesterol. The liver synthesizes about 0.5 g of bile acids per day (80–90 kg body weight) (fig. 4).

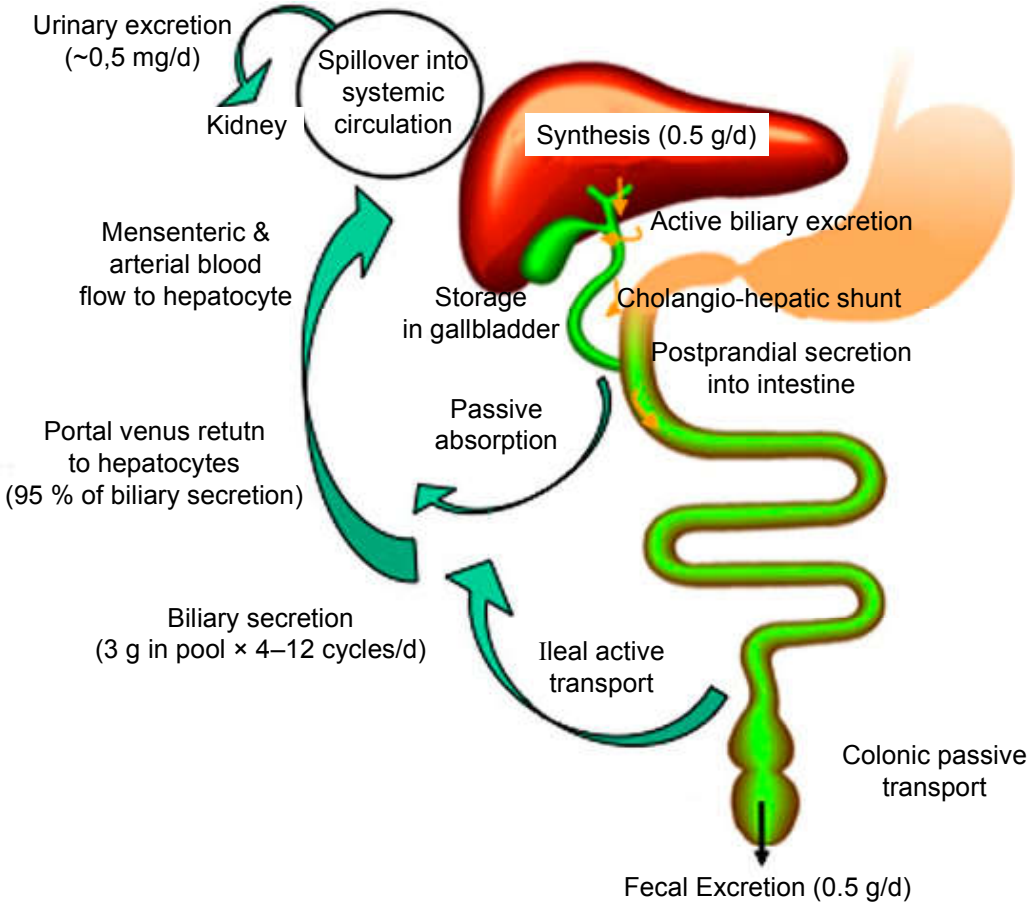


Fig. 4. Enterohepatic circulation of bile acids (Chiang J. Y. L., Ferrell J. M. Bile Acid Metabolism in Liver Pathobiology. Gene Expr. 2018)

Bile acids are secreted into canaliculi by active transport to form bile. Bile acids are stored in the gallbladder and are released after meal intake into the intestinal tract via the common bile ducts. Small amounts of bile acids are circulated back to hepatocytes via a cholangio-hepatic shunt. In the upper intestine, a small amount of bile acids is passively absorbed, but most bile acids are reabsorbed in the ileum by an active transport system to portal blood circulation and then to the liver. This enterohepatic circulation of bile acids is highly efficient and recovers about 95 % of bile acids in the pool. The small amount of bile acid lost in feces (0.5 g/day) is replenished by de novo synthesis in the liver. Enterohepatic circulation of bile acids occurs on average six to eight times a day to maintain a constant bile acid pool size of ~3 g. Bile acids (~0.5 mg/day) spilled over into the systemic circulation are excreted into the urine. (fig. 5).

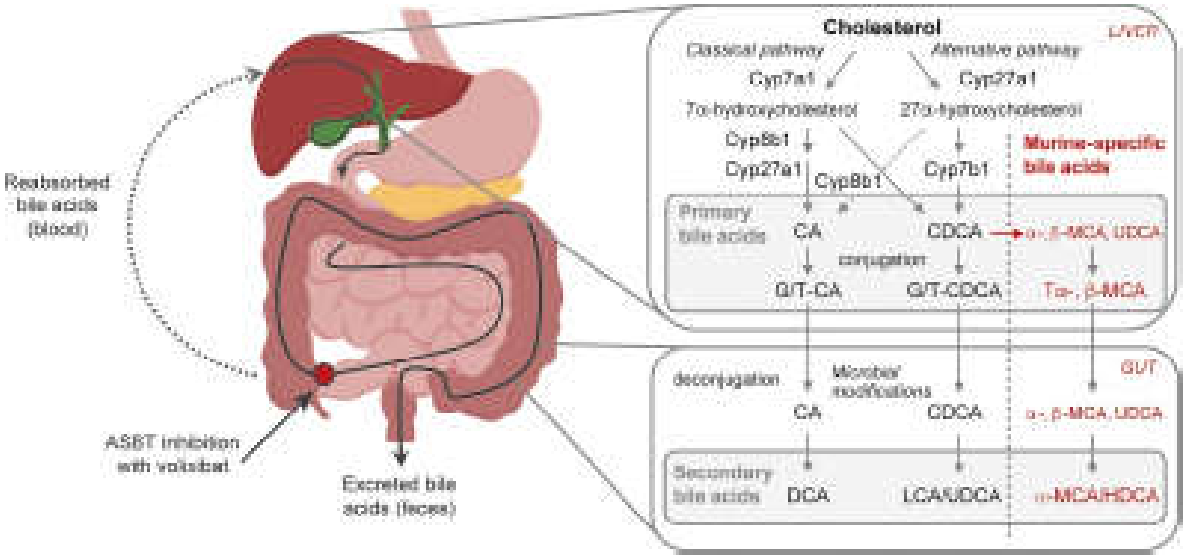


Fig. 5. Bile acid synthesis pathways (Chiang J. Y. L., Ferrell J. M. Bile Acid Metabolism in Liver Pathobiology. Gene Expr. 2018)

ASBT — apical sodium–bile acid transporter.

Volixibat, an ASBT inhibitor, is an experimental medication currently under development as a possible treatment for nonalcoholic steatohepatitis, the most severe form of non-alcoholic fatty liver disease. Another medication in the same class is elobixibat though it is not intended to treat fatty liver disease.

EPIDEMIOLOGY

The incidence of biliary tract diseases, including GD and chronic cholecystitis is high around the world (fig. 6). 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 elderlies of 60–70 years old it is 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.

Gallstone disease also carries inherent risks. Prospective population-based surveys have revealed increased overall mortality, particularly from cardiovascular disease and cancer. Further, as the incidence of gallstone disease escalates, there is a concomitant increase in complications like gallstone-related pancreatitis.

Although symptomatic and complicated stones represent only 20 % of all gallstones, they lead to clinically relevant morbidity and complications as well as high costs of medical care. Complication rates are higher in older people and in some ethnic groups and are also influenced by socio-economic factors.

Many risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female sex and family history or genetics. Conversely, the modifiable risks for cholesterol gallstones are obesity, rapid weight loss and a sedentary lifestyle. The rising epidemic of obesity and the metabolic syndrome predicts an escalation of cholesterol gallstone prevalence.

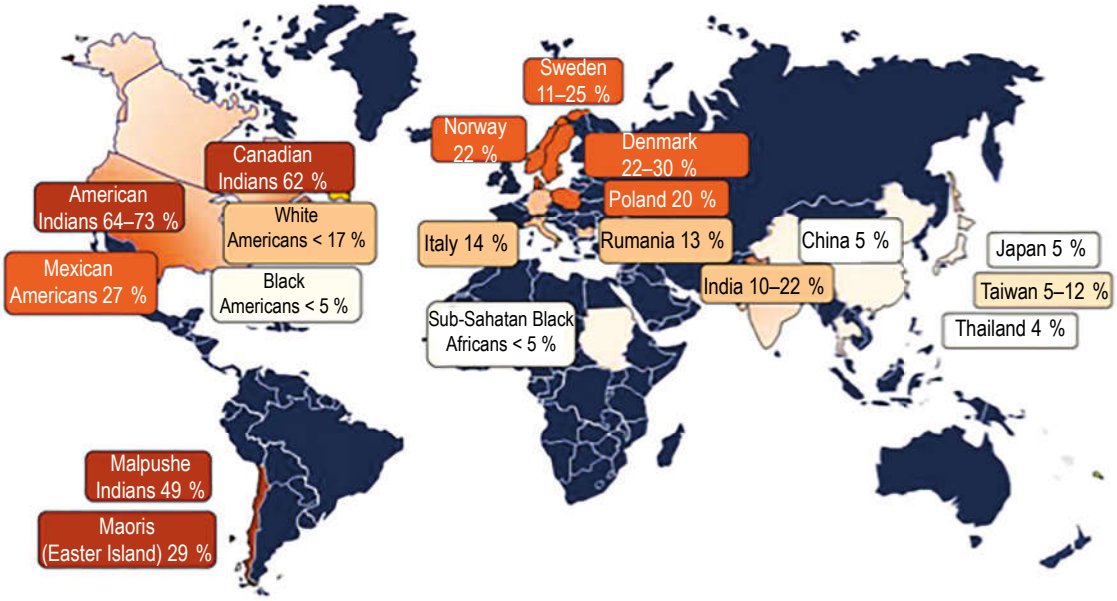


Fig. 6. Worldwide prevalence of gallstones in females based on ultrasonographic surveys (Stinton L. M., Shaffer E. A., Gut and Liver 2012)

Risk factors for biliary sludge include pregnancy and oral contraceptive pill use, drugs like ceftriaxone, octreotide and thiazide diuretics and total parenteral nutrition or fasting and rapid weight loss.

Diseases like cirrhosis, chronic hemolysis and ileal Crohn's disease are risk factors for black pigment stones. Gallstone disease in childhood, once considered rare, has become increasingly recognized with similar risk factors as those in adults, particularly obesity.

GALLSTONE DISEASE

Holelithiasis is the medical term for gallstone disease. Cholelithiasis involves the presence of gallstones, which are concretions that are formed 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 are developed 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.

Gallstone symptoms: Pain at right hypochondrium or epigastrium, often radiating to the right shoulder forcing the patient to rest and not relieved by a bowel movement. Most commonly the pain is constant, without colics. The Danish prevalence study identified «right upper quadrant pain during the night» as the most discriminating symptom in men and «strong and oppressive pain, provoked by fatty meals» as the symptom best correlating with the presence of gallstones in women [2]. Many patients present with vague indigestion and bloating which are more likely to be related to irritable bowel syndrome. However, sometimes it is very difficult to decide whether gallstones cause the symptoms or not. For example, the location of the pain is often epigastric and this may be misinterpreted as peptic ulcer disease particularly if the pain occurs after meals and at night.

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 % become symptomatic. Each year in the United States approximately 500,000 persons 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.

In Europe about 10 % of all adults have gallstones, with women having 3 times the prevalence of men during the fertile period. Overall the prevalence in women is twice that in men. The prevalence rises with age in both sexes and at the age of 65 about 30 % of women have gallstones, and by the age of 80, 60 % of both men and women have them.

Prevalence of gallstones is highest in people of northern European countries, 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 but there is an increasing prevalence trend with similar risk factors as those in adults, particularly obesity.

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 (table 1).

Table 1

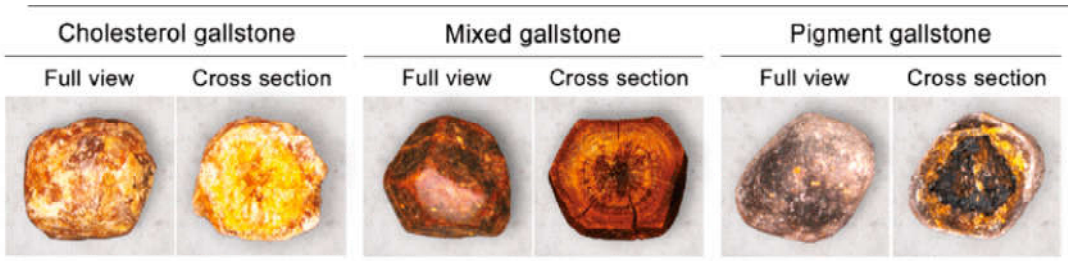
Types of Gallbladder and Biliary Tract Stones: Characteristics and Clinical Associations

	Cholesterol gallstones	**Black pigment stones**	**Brown pigment stones**	**Biliary sludge (microlithiasis)**
Compo-sition	Cholesterol (50–100 %)	Calcium bilirubinate polymer	Unconjugated bilirubin, calcium soaps of fatty acids, cholesterol & mucin	Pigment (calcium-biliru-binate), cholesterol microcrystals & mucin
Loca-tion	Gallbladder ± com-mon duct (~10 %)	Gallbladder ± com-mon duct	Bile ducts	Gallbladder
Dete-ction	Ultrasonography	Ultrasonography	Cholangi-ography	Abdominal or endoscopic ultrasonography; microscopy of bile
Clinical associ-ations	Metabolic: family history (genetic traits), obesity, female sex, aging [excessive cholesterol secretion]	Increased or altered bilirubin excretion in hemolysis, cirrhosis, cystic fibrosis, Crohn's disease, advanced age [excessive bilirubin excretion]	Infection, inflammation, infestation [stasis, strictures]	Fasting, TPN, pregnancypossible prelude to stone formation

Thus, the main factors that determine whether cholesterol gallstones will form are the amount of cholesterol secreted by liver cells, relative to lecithin and bile salts, and 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 (fig. 7). 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.

a



b

	Cholesterol gallstone (mg/%)	Mixed gallstone (mg/%)	Pigmented gallstone (mg/%)
Cholesterol	84.3 ± 5.7	62.0 ± 4.2	17.7 ± 3.9
Calcium	0.9 ± 0.2	5.6 ± 1.1	28.0 ± 2.9
Phosphate	0.2 ± 0.2	10.6 ± 1.0	18.4 ± 1.0
Bilirubin	3.0 ± 1.4	9.0 ± 0.2	18.5 ± 2.6
Triglyceride	7.2 ± 0.8	6.2 ± 0.3	6.4 ± 0.3
Bile acid	4.5 ± 0.2	7.0 ± 2.3	10.4 ± 2.3

c

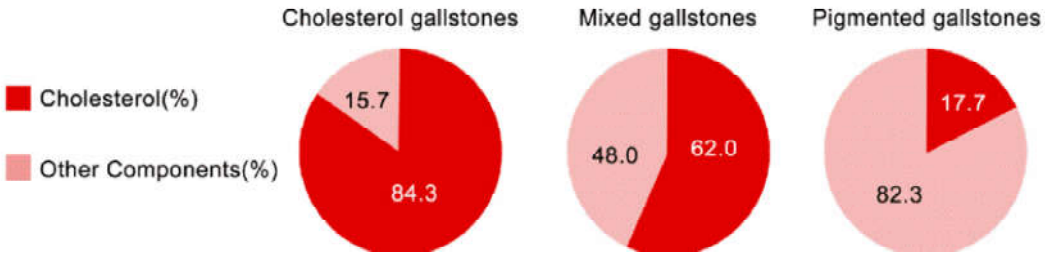


Fig. 7. Composition of gallstones:
a — appearance; *b* — composition; *c* — the cholesterol presence

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 be crystallized 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 (table 2).

Table 2

Risk factors for gallstone disease

Non-modificable	Modificable
Cholesterol gallstone	
Increasing age female sex family history ethnicity	High calorie/ high carbohydrate diet Low fibre diet pregnancy reduced physical activity obesity and the metabolic syndrome diabetes mellitus / hyperinsulinism rapid weight loss total parenteral nutrition Drugs: estrogen, progesteron, ceftiaxone, octreotide and thiazide diuretics bariatric surgery/ gastrectomy chronic hepatitis C virus infection
Pigment stones	
Age	chronic hemolysis (black stones) liver cirrhosis Crohn's disease Cystic fibrosis extensive ileal resection (black stones) Biliary infections

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:

1. The lithogenic state, in which conditions favor gallstone formation.
2. Asymptomatic gallstones.
3. Symptomatic gallstones, characterized by episodes of biliary colic.
4. 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. The presence of gallstones is detected incidentally in patients who don't have any abdominal symptoms or have symptoms that are not thought to be due to gallstones. Diagnosis is made during routine ultrasound for other abdominal conditions or, occasionally, by palpation of the gall bladder at operation. This definition implies that we know which symptoms are specific to 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 n't require any treatment.

Complication (acute pancreatitis, obstructive jaundice, cholecystitis) rates are 0.2–0.8 % per annum. The risk of developing gall bladder cancer is 0.3 % over 30 years in one study and 0.25 % for women and 0.12 % for men in another over a similar period in this group. Some studies suggest a much higher cancer risk with stones larger than 3 cm size.

Therefore, expectant management is an appropriate choice for silent gallstones in the general population.

The exception is patients at high risk for experiencing biliary complications:

1. Large gallstones (> 3 cm) or gallbladders crammed with stones that carry a higher risk of developing gallbladder cancer, perhaps an indication for prophylactic cholecystectomy.

2. Sickle cell disease is associated with the development of pigment gallstones, frequently necessitating cholecystectomy. Prophylactic cholecystectomy should be considered because stone complications are frequently difficult to distinguish from the clinical features of a sickle cell crisis or its complications such as infarction of the liver or abdominal viscera. When performed early, outside the emergency setting, cholecystectomy lessens the surgical risks, but still carries a high mortality rate of 1% and postoperative complications of > 30 %.

3. Solid-organ transplantation (heart, lung, kidney, pancreas).

Although stem cell (bone marrow) transplantation carries its own problems from cholelithiasis and biliary sludge developing, more problematic in the aftermath of solid organ transplantation in which gallstones that develop frequently progress to symptoms and complications like cholecystitis, principally during the first 2 years.

4. Abdominal surgery, performed for other reasons, may benefit from a simultaneous cholecystectomy in situations where the risk of gallstone formation and complications are high. Prophylactic cholecystectomy therefore should be considered in morbidly obese patients undergoing bariatric surgery.

Biliary colic

Since most gallstones are asymptomatic, it is essential to define exactly which symptoms are caused by gallstones: true biliary pain and/or complications, versus nonspecific abdominal complaints including dyspepsia.

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 min 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). 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 (fig. 8).

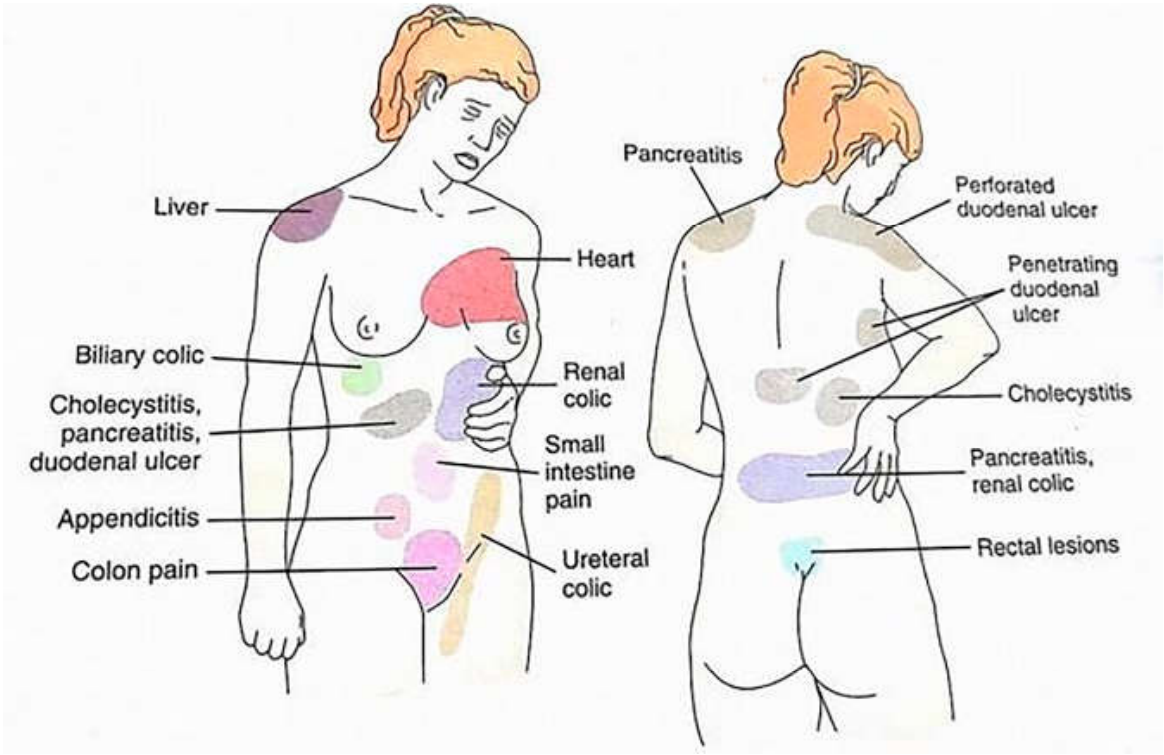


Fig. 8. Differential diagnosis of the disease by the pain location (https://en.wikipedia.org/wiki/Referred_pain)

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:

1. Uncomplicated biliary colic — Pain that is poorly localized and visceral; an essentially benign abdominal examination without rebound or guarding; absence of fever.

2. 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:

– 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 (51.3 μmol/L).

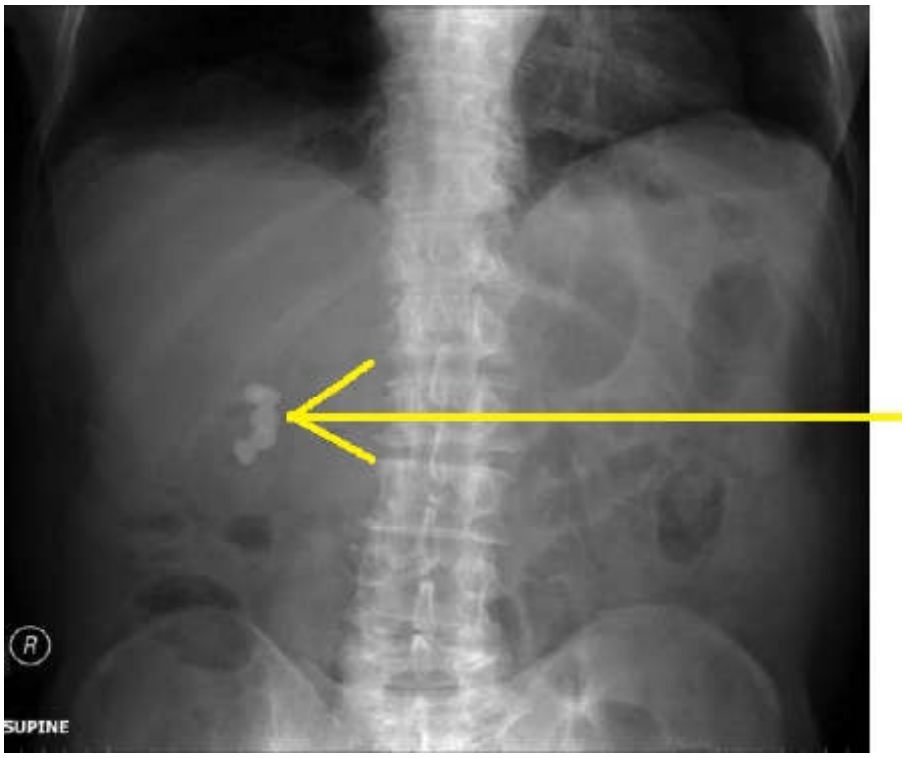
If obstruction persists, a progressive decline in the level of transaminases with rising alkaline phosphatase and bilirubin levels may be noted over several days. Prothrombin time may be elevated in patients with prolonged CBD obstruction, secondary to depletion of vitamin K (the absorption of which 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 and pancreatitis.

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 (fig. 9).

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.



Gallstones shown within the gallbladder cavity

Fig. 9. Abdominal radiography (https://www.wikidoc.org/index.php/Gallstone_disease_x_ray)

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 (abdominal tenderness from pressure of the ultrasound probe over the visualized gallbladder is more severe then from pressure of the probe elsewhere) (fig. 10).

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 (fig. 11).

Computed tomography (CT) — More expensive and less sensitive than ultrasonography for detecting gallbladder stones, but superior for demonstrating stones in the distal CBD.

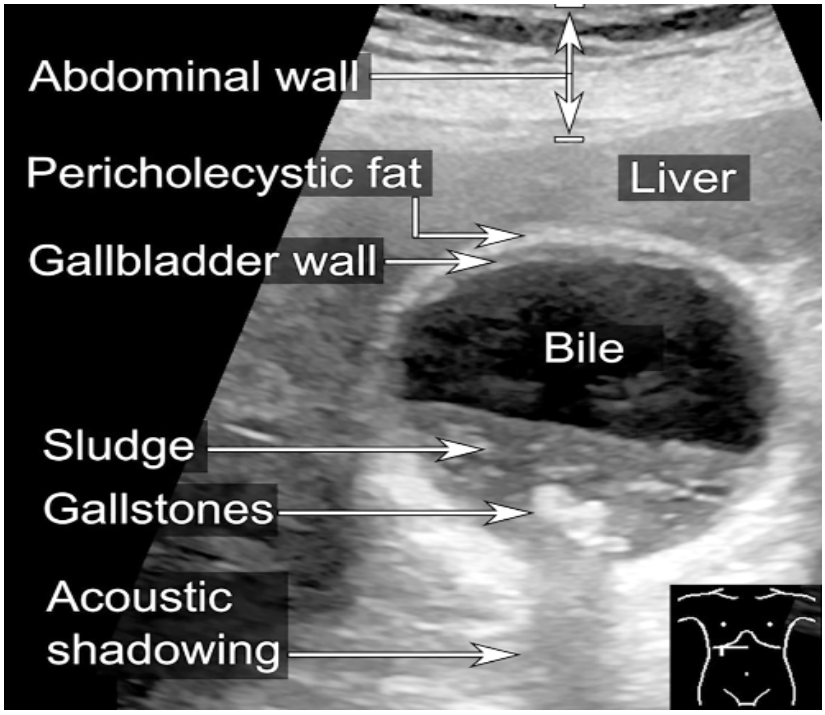


Fig. 10. Ultrasonography of sludge and gallstone (https://en.m.wikipedia.org/wiki/File:Ultrasonography_of_sludge_and_gallstones,_annotated.jpg)

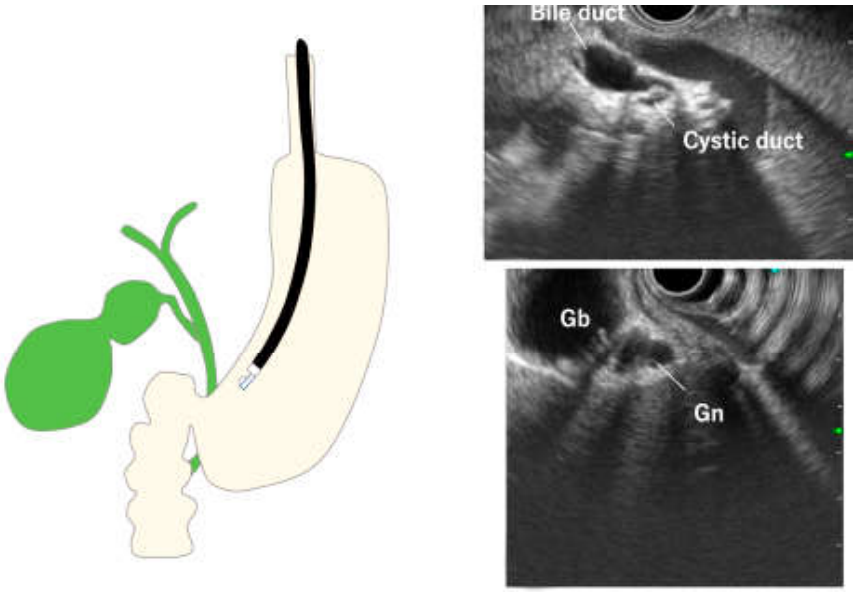


Fig. 11. Convex array (transgastric scanning). a EUS image of the cystic duct junction. b EUS image of the gallbladder neck and body. Gn: neck of gallbladder, Gb: body of gallbladder (Tanaka, K. et al. Role of endoscopic ultrasound for gallbladder disease. J Med Ultrasonics 48, 2021)

Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) — Usually reserved for cases in which choledocholithiasis is suspected.

On fig. 12 Extrahepatic bile duct is dilated with mild intrahepatic duct dilatation. Persistent filling defect within the distal common bile duct keeping with choledocholithiasis. Large stone and smaller adjacent stones in the gallbladder neck.

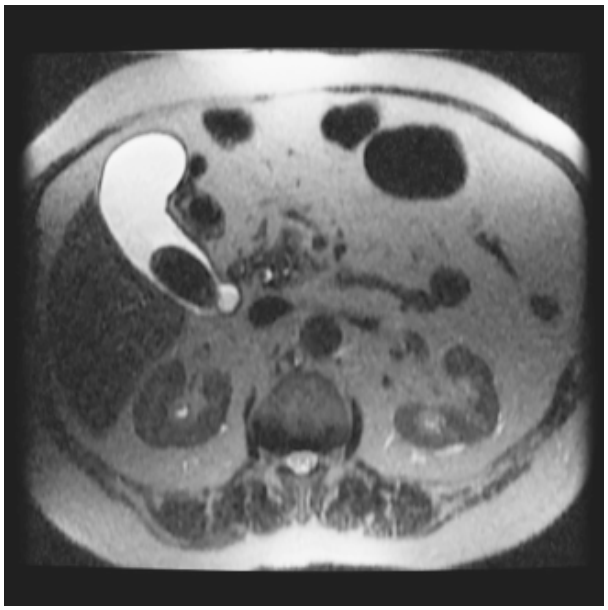


Fig. 12. Choledocholithiasis: MRCP (Knipe, H. Choledocholithiasis: MRCP. Case study. https://radiopaedia.org/cases/40046)

Percutaneous transhepatic cholangiography (PTC). Scintigraphy — Highly accurate for the diagnosis of cystic duct obstruction.

X-rays are used to examine the liver and bile ducts (fig. 13).

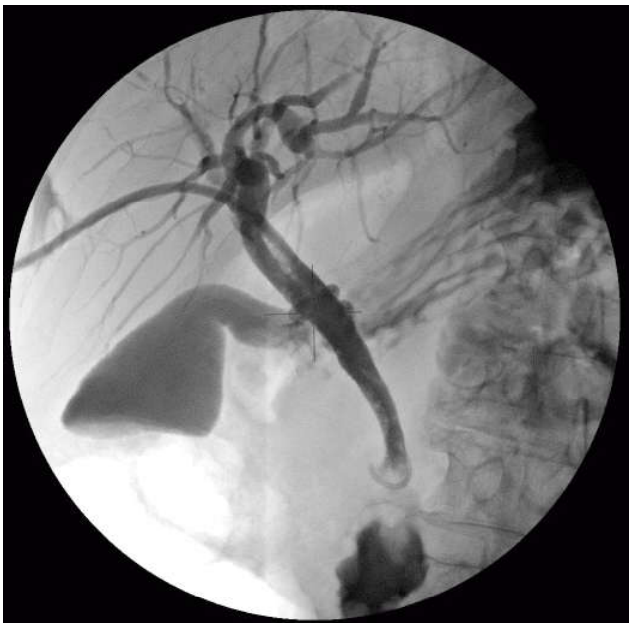


Fig. 13. Percutaneous transhepatic cholangiography (J. Guntau of German Wikipedia, an example of percutaneous transhepatic cholangiography showing the biliary tree)

Endoscopic retrograde cholangiopancreatography (ERCP) is usually performed in conjunction with endoscopic retrograde sphincterotomy and gallstone extraction.

This is accomplished by the insertion of a thin needle through the skin and into the liver carrying a contrast medium to help to see blockages in liver and bile ducts.

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 cholecys titis 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;

– 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* (fig. 10). 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 hypoechogenic limbus (edema of gallbladder wall).

2. *Cholecystography* (fig. 9):

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* (fig. 11) — can be conducted only if gallstones are absent! Helps to access 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 lamblia 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):

a) preparations that stimulate cholepoietic function of liver (choleretics):

– preparations of bile acids: cholenzym, liobilum

– synthetic preparations: oxaphenamide, 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

b) preparations that stimulate biliary excretion:

– cholekinetics (inrease 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 noriceptors 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 IV 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.

– supportive criteria such as low ejection fraction on gallbladder scintigraphy (< 40 %) and normal liver enzymes, conjugated bilirubin, and amylase/lipase can aid in diagnosis.

Do NOT use these criteria in patients with:

– atypical symptoms for biliary colic (mild, transient, constant, daily).

– visualized cholelithiasis or microlithiasis/sludge on ultrasound or endoscopic ultrasound (EUS).

– structural abnormalities, especially biliary dilation or liver enzymes not explained by other cause: should consider EUS or magnetic resonance cholangiopancreaticography (MRCP).

Critical to obtaining a detailed history of the pain pattern which is consistent with typical biliary pain criteria:

– if the pain pattern is not consistent with typical biliary pain, should investigate other causes.

– pain does not need to be localized to the right upper quadrant (frequently epigastric, non-radiating);

– overlap exists between functional gallbladder disorder and other functional GI disorders;

– with repeated episodes of biliary pain, consider microlithiasis;

– sphincter of Oddi disorder is typically and most commonly diagnosed when the gallbladder is absent. However, biliary dilatation or enzyme elevation is consistent with sphincter of Oddi disorder when the gallbladder is present

Step 1. To fulfill the Rome IV criteria for biliary pain, patient must have pain that is located in the epigastrium and/or right upper quadrant and also meets the following criteria (fig. 14):

Builds up to a steady level and lasting 30 minutes or longer.

Occurs at different intervals (not daily).

Severe enough to interrupt daily activities or lead to an emergency department visit.

Not significantly (< 20 %) related to bowel movements.

Not significantly (< 20 %) relieved by postural change or acid suppression.

*The pain may be associated with:

Nausea and vomiting.

Radiation to the back and/or right infra-subscapular region.

Waking from sleep.

Step 2. If the above criteria are met, determine if the patient meets criteria of functional gallbladder disorder or functional biliary sphincter of Oddi disorder.

Is gallbladder present?	
Step 2A: If gallbladder **present**: **Are gallstones or other structural pathology present**?	**Step 2B**: If gallbladder **absent**: **Do liver enzymes elevate during painful episodes**?
If negative: fulfills criteria for functional gallbladder disorder **Supportive criteria for functional gallbladder disorder*: – Low ejection fraction on gallbladder scintigraphy. – Normal liver enzymes, conjugated bilirubin, and amylase/lipase	**Is bile duct dilation present**? (not due to other causes, i. e. opiates) If **both** criteria met: fulfills criteria for biliary stenosis If **one** criteria met: fulfills criteria for functional biliary sphincter of Oddi disorder If **no** criteria met: fulfills criteria for functional biliary-like pain

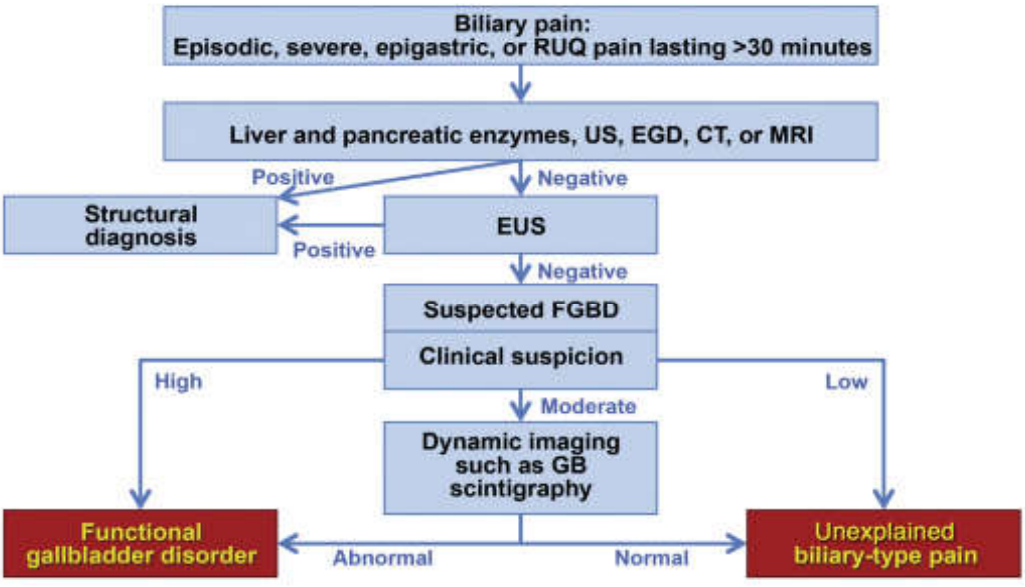


Fig. 14. Biliary pain diagnosis algorithm (Cotton P. B. et al. Rome IV. Gallbladder and Sphincter of Oddi Disorders. Gastroenterology. 2016)

If diagnostic criteria for typical biliary pain met + presence of gallstones or other structural pathology (positive):

– if gallbladder is present, refer to surgery for possible cholecystectomy;

– if gallbladder is absent, consider EUS +/– endoscopic retrograde cholangiopancreatography (ERCP).

If diagnostic criteria for typical biliary pain met + absence of gallstones, elevated liver enzymes and/or bile duct dilation:

– if gallbladder is present: consider *functional gallbladder disorder*;

– if gallbladder is absent: consider *biliary sphincter of Oddi disorder vs functional biliary pain*.

If diagnostic criteria for typical biliary pain NOT met + absence of gallstones or other structural pathology (negative): consider alternative diagnoses for gastrointestinal pain.

Management

Management should be based on the presence or absence of a gallbladder, gallstones/sludge or other structural pathology.

Functional Gallbladder Disorder (gallbladder present):

Symptoms often resolve spontaneously, advise reassurance.

Anti-spasmodics, neuromodulators, or ursodeoxycholic acid.

Sphincter of Oddi Disorder (gallbladder absent):

If liver enzymes are **elevated** during an episode **AND** the bile duct dilation not due to other causes (i. e. opiates):

Consistent with biliary stenosis.

Consider sphincterotomy.

If liver enzymes are **elevated** during an episode **OR** the bile duct dilation:

Consistent with functional biliary SOD.

Can consider sphincterotomy but risks often outweigh benefits.

Consider neuromodulation such as tricyclic antidepressants.

If liver enzymes are **normal** during an episode **AND** the bile duct is not dilated:

Consistent with functional biliary-type pain.

Avoid sphincterotomy as proven risks outweigh benefits.

Reassurance +/– neuromodulation advised.

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., cholecystokinin (CCK)-8 5 ng/kg i. v. over 10 minutes, or 50 ml $MgSO_4$ 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;

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. Laparascopic cholecystectomy retains a role in the treatment of gall bladder dysfunction, although favorable outcomes may deteriorate with time.

KNOWLEDGE CONTROL

Control of initial level of knowledge

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

a) water; c) cholesterol; e) organic matrix?
b) bile salts; d) phospholipids;

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

a) 5–10 %; c) 15–20 %; e) 40–60 %.
b) 10–15 %; d) 20–25 %;

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 ethiologic factors is the most common for the formation of chronic cholecystitis?

a) bacteria; c) lamblia; e) impaired lipid metabolism.
b) virus; d) aseptic;

8. What are the clinical symptoms typical for cholecystitis?

a) pain syndrome; c) dyspeptic; e) everything mentioned above.
b) premenstrual tension; d) solar;

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

a) hormone therapy; c) intake of fatty foods;
b) family history; 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; d) repeated vomiting, no relief;
b) bitter taste in mouth; e) excessive stool.
c) single vomiting, bringing relief;

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; c) burning; e) dull, oppressive.
b) spastic; d) mild aching;

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

a) histamine; c) magnesium sulfate; e) caffeine.
b) cholecystokinin; d) aminophylline;

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

a) rapid weight loss; c) low fat diet;
b) high fiber diet; d) pancreatitis.

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

a) hereditary predisposition; d) chronic cholecystitis;
b) impaired lipid metabolism; e) everything listed above.
c) obesity;

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

a) plain X-ray of abdomen; c) elimination diet;
b) ultrasonography; d) lipid profile.

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

a) stone blocking the neck area of galbladder;
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; c) bile; e) mucus.
b) calcium stearate; d) cholesterol;

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; d) peptic ulcer;
b) gallstone disease; e) hiatal hernia.
c) chronic pancreatitis;

2. A woman of 58 years old was delivered to the emergency room with intense pain in the upper abdomen that occured 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) biliary colic;
d) acute pancreatitis;
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 — 12.7×10^9 / 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.

Answers

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.

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Учебное издание

Алексеева Елена Сергеевна
Дрощенко Виталий Владимирович

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Учебно-методическое пособие

На английском языке

Ответственная за выпуск Е. В. Рылатко
Переводчики Е. С. Алексеева
Компьютерная вёрстка А. В. Янушкевич

Подписано в печать 15.01.24. Формат 60×84/16. Бумага писчая «Xerox Марафон Бизнес».
Ризография. Гарнитура «Times».
Усл. печ. л. 2,32. Уч.-изд. л. 1,7. Тираж 53 экз. Заказ 142.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 24.11.2023.
Ул. Ленинградская, 6, 220006, Минск.