

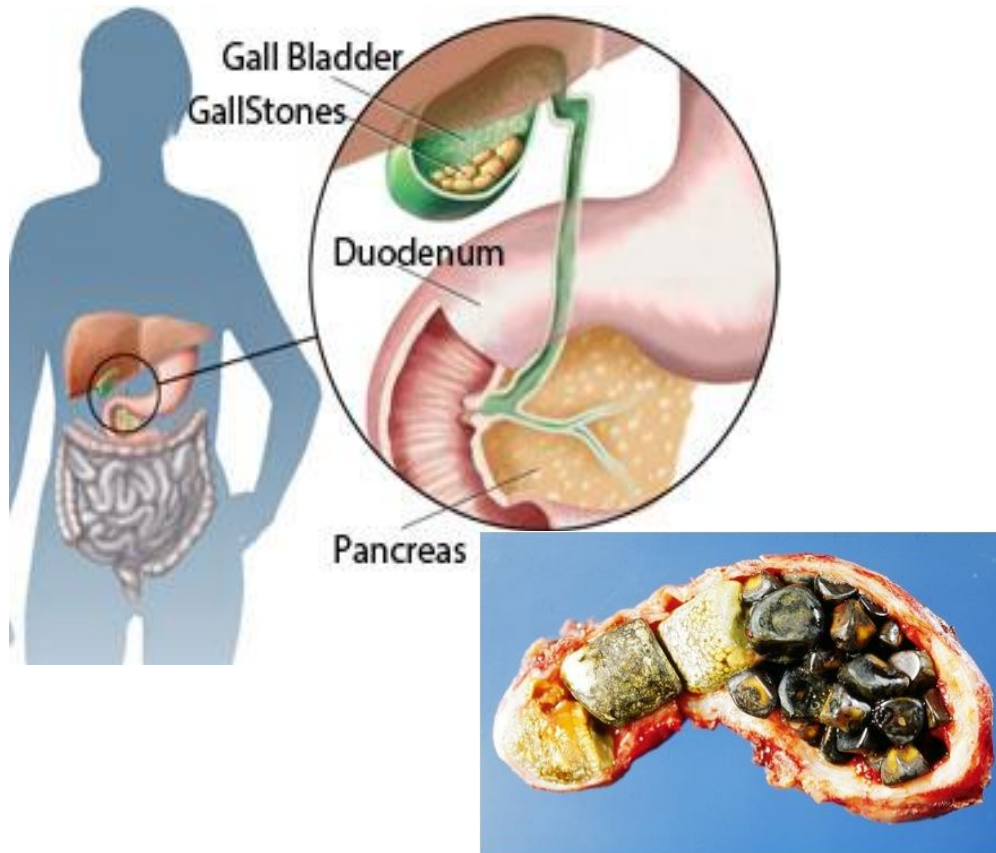
Supportive module 2: Basics of diagnosis, treatment
and prevention of major gastroenterological diseases

Cholelithiasis, Chronic Cholecystitis and Functional Biliary Disorders

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

M. Yabluchansky, L. Bogun, L. Martymianova, O. Bychkova, N. Lysenko, M. Brynza
V.N. Karazin National University Medical School' Internal Medicine Dept.

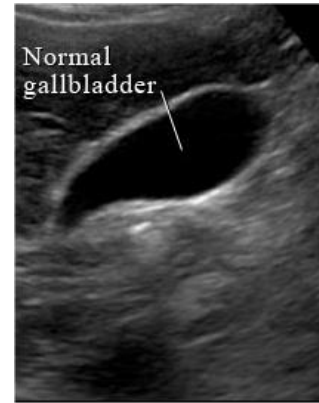
Cholelithiasis: Plan of the Lecture



- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Cholelithiasis: Definition

Cholelithiasis is the medical term for gallstone disease and means the formation and/or presence of one or more gallstones (small or large rocks or calculuses) in the gallbladder or bile ducts.



US MLE TEST

For which of the following patients is an abdominal ultrasound the most appropriate first diagnostic test?

1. 69-year-old female smoker with 10 pound weight loss and change in sputum.
2. 64-year-old male with known prostate cancer presenting with lower extremity weakness and loss of bladder control.
3. 58-year-old male with Marfan syndrome presenting with acute onset chest pain radiating to the back.
4. 28-year-old female with Crohn's disease presenting with 5 hours of abdominal pain, constipation, and nausea
5. 48-year-old mother of 3 with a history of right upper quadrant pain following fatty meals.

US MLE TEST EXPLANATION

The correct answer is 5. This patient's presentation is consistent with biliary colic. Abdominal ultrasonography is the best initial method for evaluating gallbladder pathology.

Incorrect Answers:

1: This presentation is consistent with lung cancer. The appropriate diagnostic test is a chest radiograph, 2: This presentation is consistent with spinal cord compression, likely secondary to tumor metastasis. The appropriate diagnostic test is an emergent MRI, 3: This presentation is consistent with aortic dissection. The appropriate diagnostic test is a chest radiograph, 4: This presentation is consistent with bowel obstruction. The appropriate diagnostic test is an abdominal radiograph.

Cholelithiasis: Epidemiology 1

- Cholelithiasis is a major public health problem in developed countries and affect up to 20% of the population
- Cholelithiasis is the most common gastrointestinal disorder for which patients are admitted to hospitals
- Cholesterol gallstones account for 90–95% of all gallstones

Cholelithiasis: Epidemiology 2

- Black pigment stones are the major stone type in patients with chronic hemolytic disorders or cirrhosis, although most patients with black pigment stones have neither of these conditions
- Gallstone disease is responsible for about 10,000 deaths per year in the United States.

Cholelithiasis: Risk Factors & Etiology

- Increasing age
- Increasing body mass
- Female gender
- Pregnancy Medicines, e.g. oral contraceptives, fibrates
- Family history
- Rapid weight loss, e.g. following bariatric surgery
- Hemolytic disorders, e.g. hemolytic anemia

Cholelithiasis: Mechanisms

Necessary and Sufficient Conditions 1

- Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts
- Besides a high concentration of cholesterol, two other factors are important in causing gallstones: 1) how often and how well the gallbladder contracts; 2) the presence of proteins in the liver and bile that either promote or inhibit cholesterol crystallization into gallstones

Cholelithiasis: Mechanisms

Necessary and Sufficient Conditions 2

- In addition, increased levels of the estrogen, as a result of pregnancy or hormone therapy, or the use of combined (estrogen-containing) forms of hormonal contraception, may increase cholesterol levels in bile and also decrease gallbladder movement, resulting in gallstone formation.

Cholelithiasis: Mechanisms

Main Factors 1

- The formation of gallstones is often preceded by the presence of biliary sludge, a viscous mixture of glycoproteins, calcium deposits, and cholesterol crystals in the gallbladder or biliary ducts
- Most gallstones consist largely of bile supersaturated with cholesterol, which results from the cholesterol concentration being greater than its solubility percentage, is caused primarily by its hypersecretion due to altered hepatic cholesterol metabolism

Cholelithiasis: Mechanisms

Main Factors 2

- A distorted balance between pronucleating (crystallization-promoting (mucin, a glycoprotein mixture secreted by biliary epithelial cells)) and antinucleating (crystallization-inhibiting) proteins in the bile can accelerate crystallization of cholesterol in the bile
- Loss of gallbladder muscular-wall motility and excessive sphincteric contraction also are involved in gallstone formation due to prolonged bile stasis, along with decreased reservoir function

Cholelithiasis: Mechanisms

Additional Factors 1

- The lack of bile flow causes an accumulation of bile and an increased predisposition for stone formation
- Ineffective filling and a higher proportion of hepatic bile diverted from the gallbladder to the small bile duct can occur as a result of hypomotility
- Occasionally, gallstones are composed of bilirubin, a chemical that is produced as a result of the standard breakdown of red blood cells (RBCs)

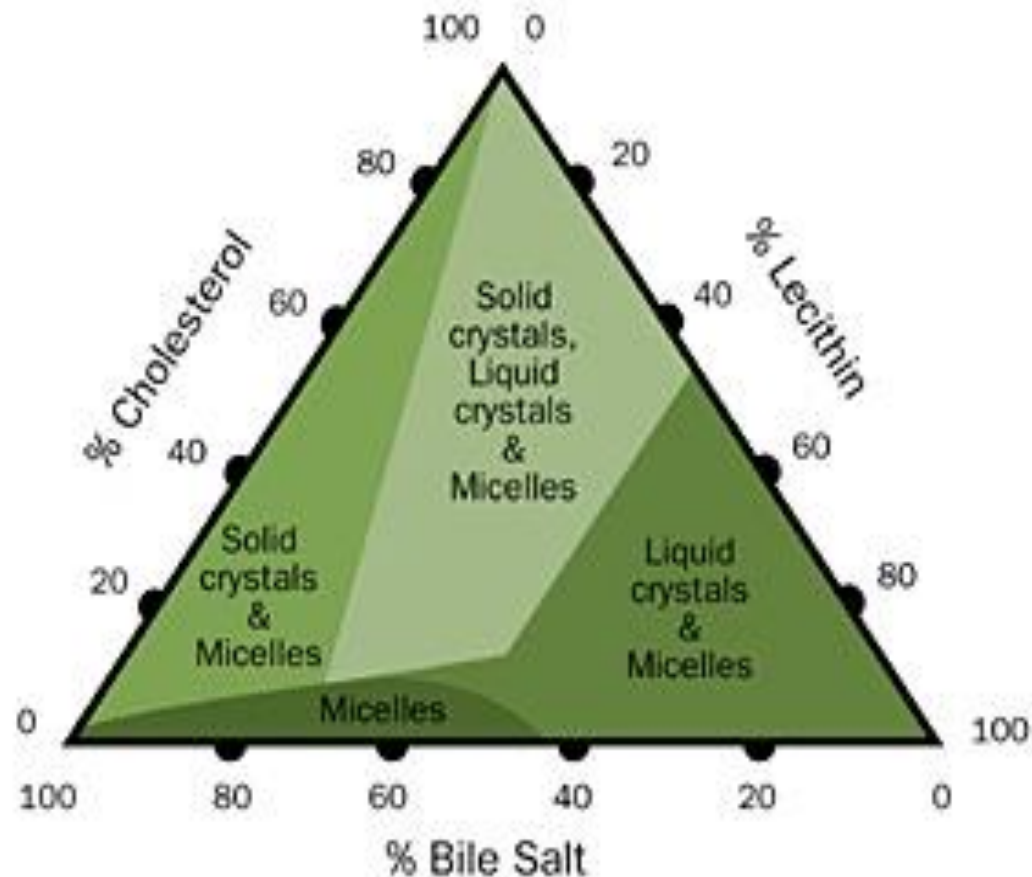
Cholelithiasis: Mechanisms

Additional Factors 2

- Infection of the biliary tract and increased enterohepatic cycling of bilirubin are the suggested causes of bilirubin stone formation, often referred to as *pigment stones*.

Cholelithiasis: Mechanisms

Composition of bile with relationships that result in the formation of gallstones



Cholelithiasis: Mechanisms

Cholesterol Gallstones 1

- 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

Cholelithiasis: Mechanisms

Cholesterol Gallstones 2

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

Cholelithiasis: Mechanisms

Calcium, bilirubin, and pigment gallstones 1

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

Cholelithiasis: Mechanisms

Calcium, bilirubin, and pigment gallstones 2

- Bile is normally sterile, but in some unusual circumstances (e.g., above a biliary stricture), it may become colonized with bacteria
- Unlike cholesterol or black pigment gallstones, which form almost exclusively in the gallbladder, brown pigment gallstones often form de novo in the bile ducts.

Cholelithiasis: Mechanisms

Mixed gallstones 1

- 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

Cholelithiasis: Mechanisms

Mixed gallstones 2

- 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.

US MLE TEST

A 30-year-old G3P3 female presents with a history of multiple episodes of right upper quadrant (RUQ) pain following fatty or heavy meals for the past year. The pain occurs in waves and resolves on its own. Her past medical history is significant for prior cholecystectomy and splenectomy, as well as two episodes of pancreatitis for which no cause was identified. Physical exam reveals an obese female in no distress, and tenderness to deep palpation in the RUQ. MRCP shows a dilated common bile duct and no other abnormalities. What course of action is most likely to lead to the correct diagnosis?

1. Blood test for anti-mitochondrial antibody,
2. Spincter of Oddi manometry,
3. Upper GI series,
4. Hydrogen breath test,
5. Capsule endoscopy.

US MLE TEST EXPLANATION

The correct answer is 2. This patient with symptoms similar to biliary colic, a history of cholecystectomy, and common bile duct (CBD) dilation in the setting of absent pancreatic masses likely has sphincter of Oddi dysfunction (SOD), and manometry of the sphincter is the best diagnostic modality for this disease.

Incorrect Answers:

1: Anti-mitochondrial antibody is associated with primary biliary cirrhosis, which is typically painless and not associated with extrahepatic ductal dilation, 3: An upper GI series would be useful for diagnosing esophageal or gastric lesions, but does not reveal pathology in the biliary tree, 4: A hydrogen breath test would be useful in diagnosing carbohydrate malabsorption, 5: Capsule endoscopy is used to diagnose luminal pathology in the small bowel, but would not reveal a stenotic or dyskinetic sphincter of Oddi.

Cholelithiasis: Classification

(International Classification of Diseases (ICD))

XI Diseases of the digestive system

K80 Cholelithiasis

K80.0 Calculus of gallbladder with acute cholecystitis

K80.1 Calculus of gallbladder with other cholecystitis

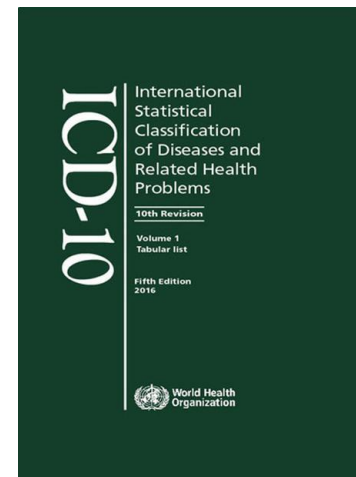
K80.2 Calculus of gallbladder without cholecystitis

K80.3 Calculus of bile duct with cholangitis

K80.4 Calculus of bile duct with cholecystitis

K80.5 Calculus of bile duct without cholangitis or cholecystitis

K80.8 Other cholelithiasis.



Cholelithiasis: Classification

Types of gallstones

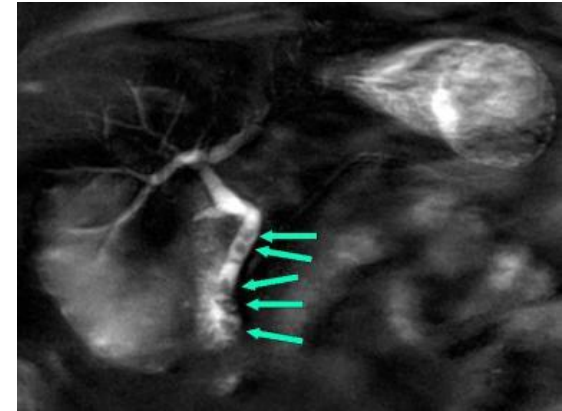


- Cholesterol gallstones: the most common type of gallstone, called a cholesterol gallstone, often appears yellow in color and are composed mainly of undissolved cholesterol, but may contain other components
- Pigment gallstones: these dark brown or black stones form when bile contains too much bilirubin.

Cholelithiasis: Classification

Stages

1. Lithogenic state, in which conditions favor gallstone formation
2. Asymptomatic ("silent") gallstones
3. Symptomatic gallstones, characterized by episodes of biliary colic
4. Complicated cholelithiasis



Magnetic resonance cholangiopancreatography (MRCP) showing 5 gallstones in the common bile duct (arrows). In this image, bile in the duct appears white; stones appear as dark-filling defects.

Cholelithiasis: Signs and Symptoms

Modalities 1

- Gallstones are generally asymptomatic
- In the uncommon event that a patient develops symptomatic cholelithiasis, presentation can range from mild nausea or abdominal discomfort to biliary colic and jaundice
- A patient with cholelithiasis also may exhibit Murphy's sign (discomfort so severe that the patient stops inspiring during palpation of the gallbladder) or jaundice

Cholelithiasis: Signs and Symptoms

Modalities 2

- Other nonspecific symptoms, such as indigestion, intolerance to fatty or fried foods, belching, and flatulence, may also be present.

Cholelithiasis: Signs and Symptoms

Biliary Colic 1

- Sporadic and unpredictable episodes
- Pain that is localized to the epigastrium or right upper quadrant, sometimes radiating to the right scapular tip
- Pain that begins postprandially, is often described as intense and dull, typically lasts 1-5 hours, increases steadily over 10-20 minutes, and then gradually wanes

Cholelithiasis: Signs and Symptoms

Biliary Colic 2

- Pain that is constant; not relieved by emesis, antacids, defecation, flatus, or positional changes; and sometimes accompanied by diaphoresis, nausea, and vomiting
- Nonspecific symptoms (e.g., indigestion, dyspepsia, belching, or bloating)

Cholelithiasis: Signs and Symptoms

Jaundice 1

- Jaundice, a yellow discoloration of the skin and the sclera of the eyes, occurs when the common bile duct is obstructed because of an impacted stone in Hartmann's pouch (Mirizzi's syndrome)



Cholelithiasis: Signs and Symptoms

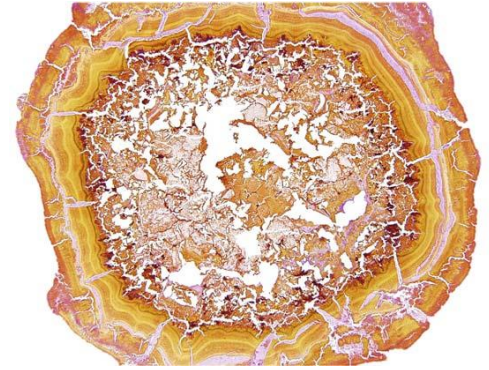
Jaundice 2

- 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 common bile duct (CBD) or common hepatic duct, resulting in obstruction and jaundice.



Cholelithiasis: History

- Key factors include female sex, obesity (BMI ≥ 30), Native American/Hispanic ethnicity, positive family history, dietary insufficiencies, use of certain medications (e.g., exogenous estrogen, octreotide, clofibrate, ceftriaxone), terminal ileum disease, pregnancy, and diabetes.



A
photomicrograph
(100x) of a
hematoxylin- and
eosin-stained
gallstone within
the gallbladder of
a golden lion
tamarin.

Cholelithiasis: Physical Exam 1

- Patients with the lithogenic state or asymptomatic gallstones have no abnormal findings on physical examination.
- Since the gallbladder is not inflamed in uncomplicated biliary colic, the pain is poorly localized and visceral in origin, fever is absent

Cholelithiasis: Physical Exam 2

- The presence of fever, persistent tachycardia, hypotension, or jaundice necessitate a search for complications of cholelithiasis, including cholecystitis, cholangitis, pancreatitis, or other systemic causes
- Choledocholithiasis with obstruction of the common bile duct produces cutaneous and scleral icterus that evolves over hours to days as bilirubin accumulates

Cholelithiasis: Physical Exam 3

- In severe cases of acute cholecystitis, ascending cholangitis, or acute pancreatitis, bowel sounds are often absent or hypoactive.

Cholelithiasis: Complications

Gallbladder Stones 1

- Acute cholecystitis occurs when persistent stone impaction in the cystic duct causes the gallbladder to become progressively inflamed
- When overgrowth of colonizing bacteria and accumulation of pus in the gallbladder (empyema) occur, the gallbladder wall may become necrotic, resulting in perforation and pericholecystic abscess

Cholelithiasis: Complications

Gallbladder Stones 2

- Chronically, gallstones may cause progressive fibrosis of the gallbladder wall and loss of gallbladder function, termed chronic cholecystitis
- Gallbladder adenocarcinoma is an uncommon cancer that usually develops in the setting of gallstones
- Occasionally, a large stone may erode through the wall of the gallbladder into an adjacent viscus (typically the duodenum), producing a cholecystoenteric fistula

Cholelithiasis: Complications

Common Bile Duct Stones 1

- Stones in the common bile duct may be asymptomatic, but, more commonly, they impact distally in the ampulla of Vater, that produce biliary colic indistinguishable from that caused by cystic duct stones
- Because impaction of common bile duct stones occludes the flow of bile from the liver to the intestine, pressure rises in the intrahepatic bile ducts, leading to elevation of liver enzymes and jaundice

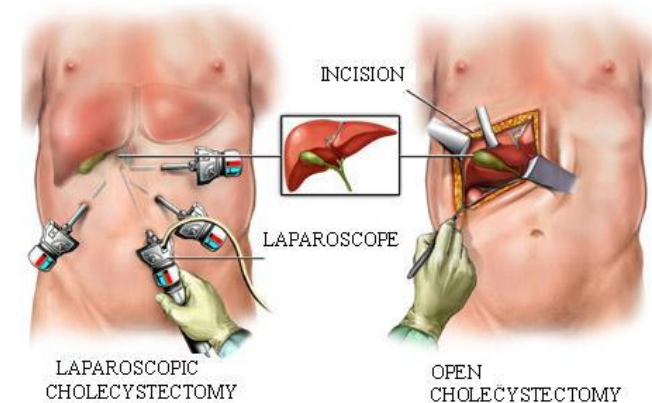
Cholelithiasis: Complications

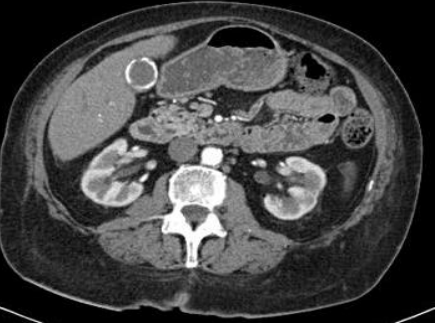
Common Bile Duct Stones 2

- Bacterial overgrowth in stagnant bile above an obstructing common duct stone produces purulent inflammation of the liver and biliary tree, termed ascending cholangitis; patients may rapidly develop septic shock unless the ductal obstruction is relieved
- A stone impacted in the ampulla of Vater may transiently obstruct the pancreatic duct, leading to in situ activation of pancreatic proteases and triggering an attack of acute pancreatitis.

Cholelithiasis: Red flags for people

- Biliary colic that cannot be effectively controlled with analgesia
- Obstructive jaundice
- Suspected acute cholecystitis
- Cholangitis
- Acute pancreatitis

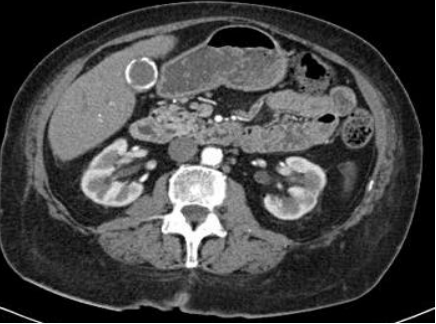




US MLE TEST

A 46-year-old female presents with severe postprandial right upper quadrant pain. She has had similar symptoms off and on for the last several years with the pain remitting after approximately a day. She undergoes an abdominal CT scan which is shown in Figure. Based on the imaging findings, this patient is at increased risk for which of the following conditions?

1. Pancreatic carcinoma.
2. Gallbladder carcinoma.
3. Hepatocellular carcinoma.
4. Aneurysm rupture.
5. Echinococcal cyst rupture.



S MLE TEST EXPLANATION

The correct answer is 2. The patient in this vignette most likely has chronic biliary colic with gallbladder calcifications (porcelain gallbladder). This condition puts the patient at increased risk of gallbladder carcinoma.

Incorrect Answers:

- 1: Calcifications of the pancreas are a mark of chronic pancreatitis. The calcifications in this scan are not of pancreatic origin.
- 3: Hepatocellular carcinoma is not a sequela of a porcelain gallbladder.
- 4: Aneurysm rupture is not a sequela of a porcelain gallbladder.
- 5: Echinococcal cysts can be detected as calcifications, but the scan in this vignette shows gallbladder calcifications.

Cholelithiasis: Diagnosis 1

- CBC, liver-function testing (ALT, AST, alkaline phosphatase; PT, INR, albumin, and bilirubin), serum amylase and lipase should be included in the laboratory tests to help discriminate between the various types of gallbladder disease and/or identify complications caused by gallbladder disease

Cholelithiasis: Diagnosis 2

- The diagnosis can be confirmed via a number of different imaging techniques: ultrasonography detects more than 90% of gallstones, computed tomography (CT) detects 75% of gallstones, magnetic resonance cholangiopancreatography (MRCP) detects approximately 98% of gallstones
- If choledocholithiasis is suspected, endoscopic retrograde cholangiopancreatography (ERCP) may be beneficial.

Cholelithiasis: Diagnosis

Laboratory Values

| Disease Abnormal | Laboratory Values |
|-----------------------|---|
| Biliary colic | No significant changes in laboratory data; acute pain may present with elevated liver enzymes and bilirubin |
| Choledocholithiasis | Elevated liver enzymes and bilirubin |
| Pancreatic gallstones | Elevated amylase and lipase; abnormal liver-function test |
| Acute cholecystitis | Leukocytosis; mild elevation in bilirubin and/or alkaline phosphatase |
| Chronic cholecystitis | Laboratory values often normal |

Cholelithiasis: Diagnosis

Transabdominal Ultrasonography



Common bile duct stone (choledocholithiasis).

Cholelithiasis: Diagnosis

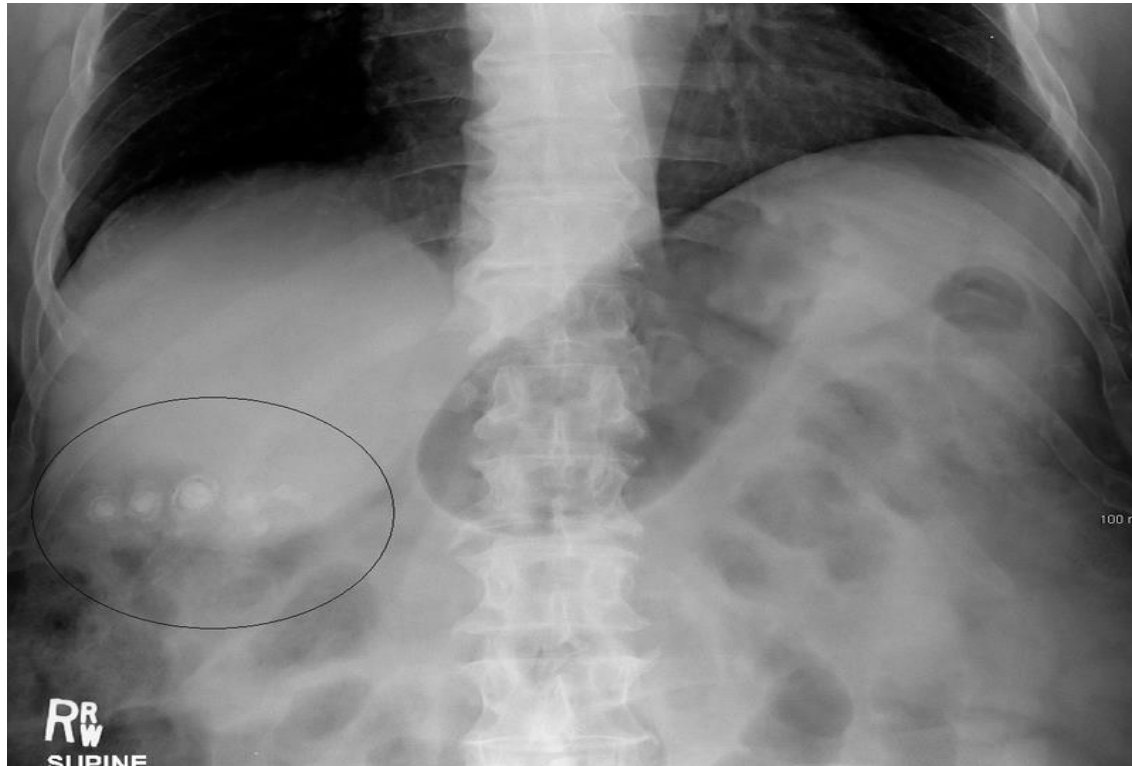
Transabdominal Ultrasonography



Cholelithiasis. Ultrasound image obtained with a 4-MHz transducer demonstrates a stone in the gallbladder neck with typical acoustic shadow.

Cholelithiasis: Diagnosis

Plain X-ray



Gallstones.

Cholelithiasis: Diagnosis

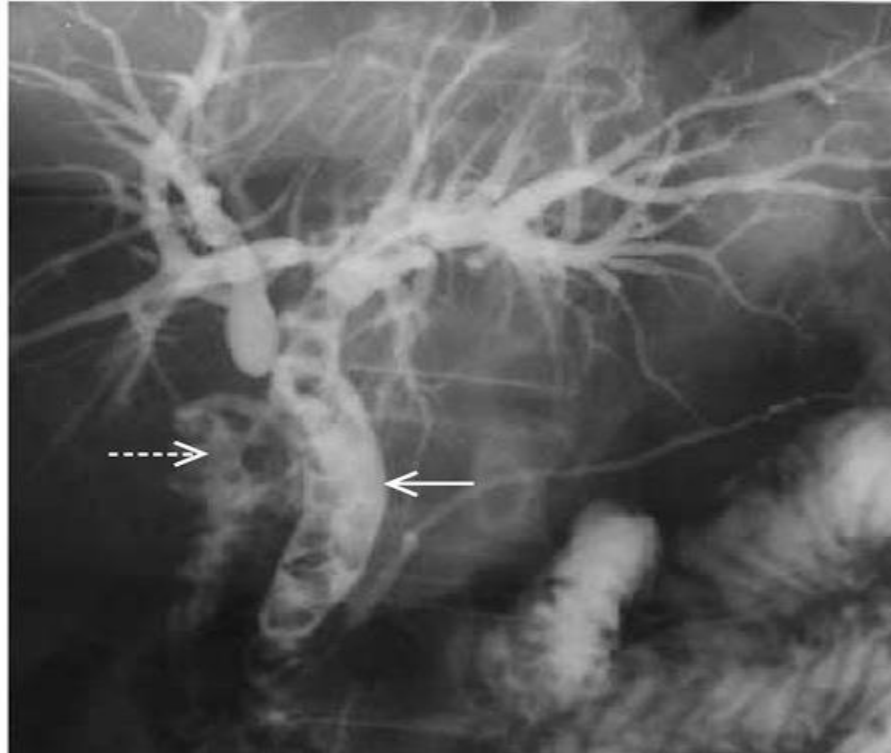
Computed Tomography



Gallstones.

Cholelithiasis: Diagnosis

Transabdominal Ultrasonography



Endoscopic retrograde cholangiopancreatography reveals abnormalities in a patient with gallstones.

Cholelithiasis: Differential Diagnosis

- Acute pancreatitis
- Appendicitis
- Bile duct strictures
- Bile duct tumors
- Cholangiocarcinoma
- Cholecystitis
- Emergent treatment of gastroenteritis
- Gallbladder cancer
- Pancreatic cancer
- Peptic ulcer disease



Cholelithiasis: Management

Lifestyle Management 1

- The patient's dietary history may indicate foods that are triggers for biliary colic which can then be avoided, e.g. fatty food
- A high-fibre diet is associated with a reduced risk of gallstone formation and it is possible that making dietary changes will improve the patient's symptoms

Cholelithiasis: Management

Lifestyle Management 2

- Paradoxically, for patients on a low-calorie diet the consumption of 10 g of fat per day has been shown to prevent gallstone formation, most likely by promoting gallbladder emptying
- Coffee and moderate amounts of alcohol have also a protective effect against biliary colic.

Cholelithiasis: Management

Patient Education

- Patients with asymptomatic gallstones should be educated to recognize and report the symptoms of biliary colic and acute pancreatitis
- Alarm symptoms include persistent epigastric pain lasting for greater than 20 minutes, especially if accompanied by nausea, vomiting, or fever
- If pain is severe or persists for more than an hour, the patient should seek immediate medical attention.

Cholelithiasis: Management

Not Only Interventional Therapy 1

- Patients experiencing asymptomatic cholelithiasis do not require treatment
- The treatment of choice for symptomatic cholelithiasis currently is laparoscopic cholecystectomy, whereas previously it was open cholecystectomy

Cholelithiasis: Management

Not Only Interventional Therapy 2

- In patients who are unable or unwilling to undergo surgery, endoscopic decompression by internal gallbladder stent can help prevent complications from developing and can serve as palliative long-term treatment
- Nonoperative therapy, which includes dissolution of gallstones using oral bile acids and shock wave lithotripsy, may be another option in such patients.

Cholelithiasis: Management

Nonoperative Therapy 1

- Nonoperative therapy is time consuming and is associated with high cost, low effectiveness, and a high recurrence rate
- Oral bile acids used for the dissolution of gallstones include chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid (ursodiol)
- Oral bile acids are most effective for small gallstones (0.5–1 cm) and may take up to 24 months to clear the stones

Cholelithiasis: Management

Nonoperative Therapy 2

- Ursodiol is the most commonly used oral bile acid, secondary to its safer side-effect profile compared with chenodiol
- Chenodiol is associated with dose-dependent diarrhea as well as with hepatotoxicity, hypercholesterolemia, and leukopenia, all of which limit its use.

Cholelithiasis: Management

Oral Bile Acid Dissolution Agents

| Agent | Dosage | Therapy Duration | Adverse Effects (>10%) |
|------------|--|--|--|
| Urso-diol | 8–10 mg/kg/day (in 2–3 divided doses); prophylaxis: 300 mg bid | Symptom relief occurs in 3–6 week; results may take 6–24 month | Headache, dizziness, diarrhea, constipation, dyspepsia, nausea, vomiting, back pain, upper respiratory tract infection |
| Cheno-diol | Initial 250 mg bid for 2 wk; increase by 250 mg/day per week until 13–16 mg/kg/day | Discontinue therapy if no dissolution has occurred in 18 month | Hypercholesterolemia, dose-dependent diarrhea, leukopenia, increased serum aminotransferase |

Cholelithiasis: Management

Analgesic 1

- NSAIDs are the preferred class of analgesia for biliary colic in patients with severe pain and those treated in the Emergency Department
- Before prescribing NSAIDs for upper abdominal pain consider if the patient's pain may have another cause, e.g. peptic ulcer disease, for which NSAIDs are contraindicated

Cholelithiasis: Management

Analgesic 2

- In practice it may be necessary to provide multiple analgesics to patients who are in severe pain
- Codeine and paracetamol may be an effective alternative to NSAIDs in patients with moderate biliary colic (a combination product of paracetamol 500 mg with codeine 30 mg)
- Morphine 5 – 10 mg, Intramuscularly, is an alternative treatment in patients with severe pain due to biliary colic and for patients when an NSAID is unsafe or fails to provide effective pain relief.

Cholelithiasis: Management

Antispasmodics and Antiemetics

- Antispasmodic medicines, e.g. hyoscine butylbromide, often in combination with an NSAID or opioid, are produce effective analgesia in some patients with biliary colic, however, other patients may not gain any benefit
- For patients that experience ongoing nausea once their pain has been controlled, antiemetics such as metoclopramide, cyclizine and ondansetron may be considered

Cholelithiasis: Prognosis 1

- Less than half of patients with gallstones become symptomatic
- The mortality rate for an elective cholecystectomy is 0.5% with less than 10% morbidity
- The mortality rate for an emergent cholecystectomy is 3-5% with 30-50% morbidity

Cholelithiasis: Prognosis 2

- Following cholecystectomy, stones may recur in the bile duct Separately, single-incisional laparoscopic cholecystectomy appears to be associated with an incisional hernia rate of 8%, with age (≥ 50 years) and body mass index (BMI) (≥ 30 kg/m²) as independent predictive factors
- Approximately 10-15% of patients have an associated choledocholithiasis.

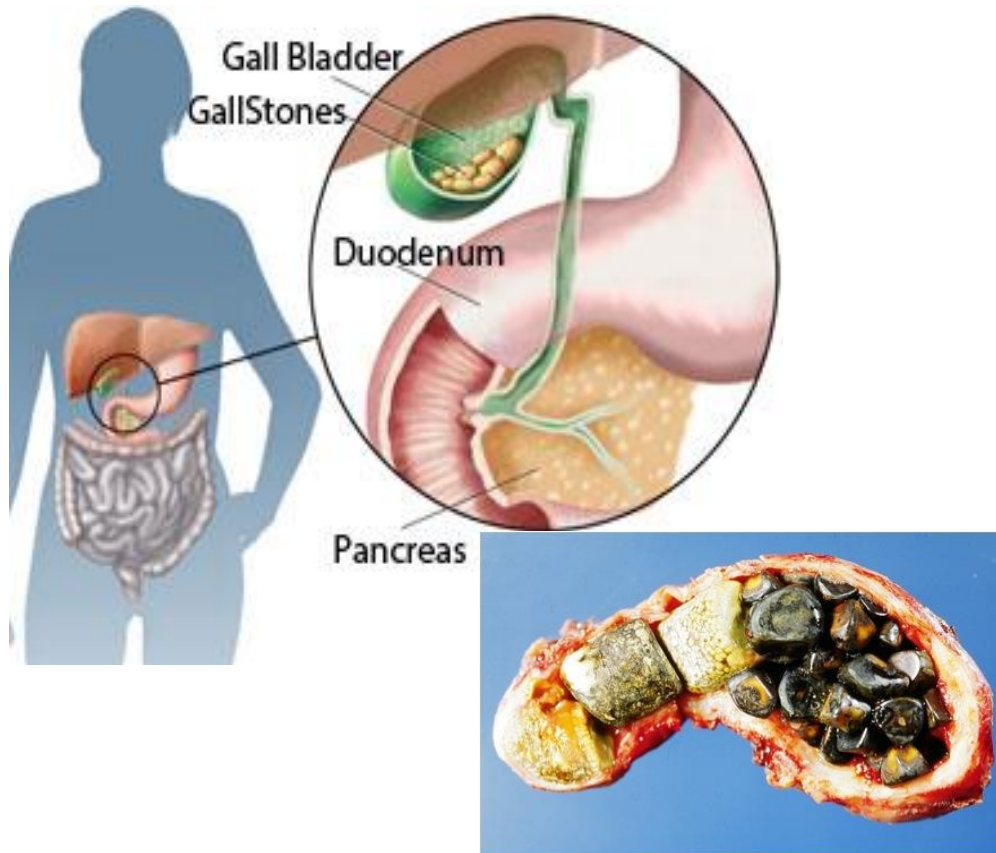
Cholelithiasis: Prophylaxis 1

- Nutrition and lifestyle changes may be beneficial for the prevention and treatment of cholelithiasis
- Because obesity is associated with an increased risk of cholelithiasis, weight loss may help prevent gallstone formation, however, excessively rapid weight loss may promote gallstone formation

Cholelithiasis: Prophylaxis 2

- Dietary factors that may help prevent gallstone formation include polyunsaturated fat, monounsaturated fat, fiber, and caffeine
- Fish oil and moderate alcohol consumption have been shown to lower triglycerides, lessen bile cholesterol saturation, and increase high-density lipoprotein (HDL).

Chronic Cholecystitis: Plan of the Lecture



- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Chronic Cholecystitis: Definition 1

- 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)
- Chronic cholecystitis is inflammation and irritation of the gallbladder that persists over time and occurs after repeated episodes of acute cholecystitis almost always due to gallstones

Chronic Cholecystitis: Definition 2

- Chronic cholecystitis may be asymptomatic, may present as a more severe case of acute cholecystitis, or may lead to a number of complications such as gangrene, perforation, or fistula formation
- Xanthogranulomatous cholecystitis (XGC) is a rare form of chronic cholecystitis which mimics gallbladder cancer although it is not cancerous.



US MLE TEST

A 41-year-old woman presents to the emergency department with severe, sudden-onset abdominal pain. She points to the right upper quadrant of her abdomen when asked to localize the pain. The pain began approximately 30 minutes after she had eaten lunch. Her vital signs are as follows: T 38.1, HR 99, BP 144/87, RR 22, O2 Sat 96% RA. An abdominal ultrasound is conducted and is shown in Figure. Upon review of her medication list, which of the following agents could have most likely increased this patient's risk for developing her presenting condition?

1. Prednisone,
2. Meperidine,
3. Naproxen,
4. Estradiol,
5. Trimethoprim-sulfamethoxazole.



MLE TEST EXPLANATION

The correct answer is 4. This patient's presentation is consistent with a diagnosis of acute cholecystitis. Elevated female sex hormones and hormonal replacement therapy are risk factors for cholecystitis.

Incorrect Answers:

1: Steroids, such as prednisone, do not increase the risk of developing acute cholecystitis, 2: Meperidine is the pain medication of choice in treating acute cholecystitis, as, unlike morphine, it does not increase muscle tone at the sphincter of Oddi, 3: NSAIDs, such as naproxen, have been shown to reduce the secretion of gallbladder mucin and thereby decrease the risk of developing gallstones and their ensuing complications, 5: Gallbladder disease is not a known side-effect of the antibiotic TMP-SMX.

Chronic Cholecystitis:

Epidemiology

Cholecystitis is relatively common condition. Approximately one-third of people with gallstones develop cholecystitis.

| | Male (Odds ratio) | | Female (Odds ratio) |
|--------------------------------------|----------------------|--------------------------------------|------------------------|
| Hypotension | 20.649 | Asthma/COPD | 18.156 |
| Insomnia | 16.098 | Depression | 17.308 |
| Chronic low back pain | 15.912 | Urinary incontinence | 16.562 |
| Asthma/COPD | 15.238 | Chronic low back pain | 15.770 |
| Urinary tract calculi | 14.877 | Lower limb varicosis | 15.323 |
| Chronic cholecystitis/ gallstones | 14.359 | Urinary tract calculi | 15.155 |
| Arthrosis | 13.957 | Insomnia | 14.881 |
| Liver disease | 13.815 | Neuropathies | 14.088 |
| Prostatic hyperplasia | 13.504 | Arthrosis | 13.564 |
| Rheumatoid arthritis | 13.408 | Liver disease | 12.636 |
| Depression | 12.409 | Rheumatoid arthritis | 11.617 |
| Neuropathies | 12.106 | Chronic cholecystitis/ gallstones | 11.415 |
| Cardiac valve disorders | 11.051 | Thyroid dysfunction | 11.390 |
| Renal insufficiency | 10.788 | Osteoporosis | 10.845 |
| Cancers | 10.679 | Chronic ischemic heart disease | 10.422 |
| Thyroid dysfunction | 10.425 | Lipid metabolism disorders | 10.046 |

Distribution and types of multiple chronic conditions in Korea.

Chronic Cholecystitis: Risk Factors & Etiology 1

- Risk factors and etiology for cholecystitis mirror those for cholelithiasis and include increasing age, female sex, certain ethnic groups, obesity or rapid weight loss, drugs, and pregnancy
- Although bile cultures are positive for bacteria in 50-75% of cases, bacterial proliferation may be a result of cholecystitis and not the precipitating factor

Chronic Cholecystitis: Risk Factors & Etiology 2

- Acalculous cholecystitis is related to biliary stasis, including debilitation, major surgery, severe trauma, sepsis, long-term total parenteral nutrition (TPN), prolonged fasting, cardiac events, sickle cell disease, *Salmonella* infections, diabetes mellitus, cytomegalovirus, cryptosporidiosis, or microsporidiosis infections in patients with AIDS.

Chronic Cholecystitis: Mechanisms 1

- 90% of cases of cholecystitis involve stones in the gallbladder (i.e., calculous cholecystitis), with the other 10% of cases representing acalculous cholecystitis
- Calculous cholecystitis is caused by obstruction of the cystic duct, leading to distention of the gallbladder



Chronic Cholecystitis: Mechanisms 2

- Although the exact mechanism of acalculous cholecystitis is unclear, injury may be the result of retained concentrated bile, an extremely noxious substance.



Chronic Cholecystitis: Classification

International Classification of Diseases (ICD)

XI Diseases of the digestive system

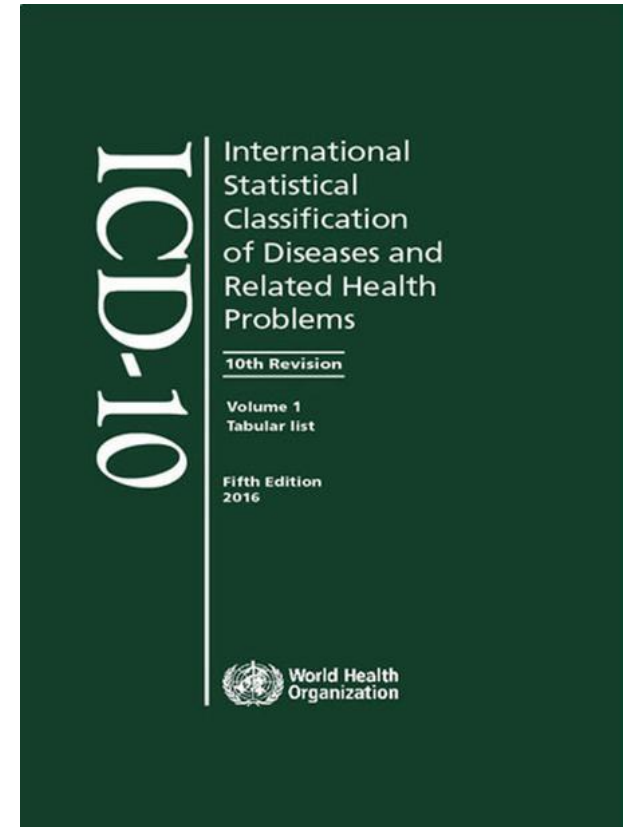
K81 Cholecystitis

K81.0 Acute cholecystitis

K81.1 Chronic cholecystitis

K81.8 Other cholecystitis

K81.9 Cholecystitis, unspecified



Chronic Cholecystitis: Classification

Clinical 1

The presence of concretions are distinguished:

- chronic cholecystitis without cholelithiasis (calculous)
- chronic calculous cholecystitis

Isolated stage:

- exacerbation
- of remission

Clinical variants:

- Cardiac (cardiac arrhythmias, ECG changes (T wave))
- Arthritic (arthralgia)

Chronic Cholecystitis: Classification

Clinical 2

Clinical variants:

- Low-grade (prolonged low-grade fever (37-38 °C) for about 2 weeks with symptoms of intoxication)
- Neurasthenic (neurasthenia and vegetative nervous dystonia in the form of weakness, malaise, irritability, insomnia)
- Hypothalamic (paroxysms of tremor, increased blood pressure, symptoms of angina, paroxysmal tachycardia, muscular weakness, hyperhidrosis).

Chronic Cholecystitis: Signs and Symptoms

1

- Most people do not have symptoms
- The symptoms of cholecystitis are similar to biliary colic but the pain becomes more severe and constant
- Pain with deep inspiration leading to termination of the breath while pressing on the right upper quadrant of the abdomen usually causes pain (Murphy's sign)
- In addition to abdominal pain, right shoulder pain can be present

Chronic Cholecystitis: Signs and Symptoms

2

- Nausea is common and vomiting occurs in 75% of all cases
- Because of the inflammation, a gallbladder size can be felt from the outside of the body in 25-50% of people with cholecystitis
- Jaundice may occur but is usually mild
- Fever is common.

Chronic Cholecystitis: History 1

- The most common presenting symptom of cholecystitis is upper abdominal
- Nausea and vomiting are generally present, and patients may report fever
- Most patients describe a history of biliary pain
- Some patients may have documented gallstones

Chronic Cholecystitis: History 2

- Acalculous biliary colic also occurs, most commonly in young to middle-aged females
- Cholecystitis is differentiated from biliary colic by the persistence of constant severe pain for more than 6 hours.

Chronic Cholecystitis: Physical Exam 1

- The physical examination may reveal fever, tachycardia, and tenderness in the right upper quadrant (RUQ) or the epigastric region, often with guarding or rebound
- The Murphy sign is described as tenderness and an inspiratory pause elicited during palpation of the RUQ

Chronic Cholecystitis: Physical Exam 2

- A palpable gallbladder or fullness of the RUQ is present in 30-40% of cases
- Jaundice may be noted in approximately 15% of cases
- The absence of physical findings does not rule out the diagnosis of cholecystitis
- Elderly patients and patients with diabetes frequently have atypical presentations, including absence of fever and localized tenderness with only vague symptoms.

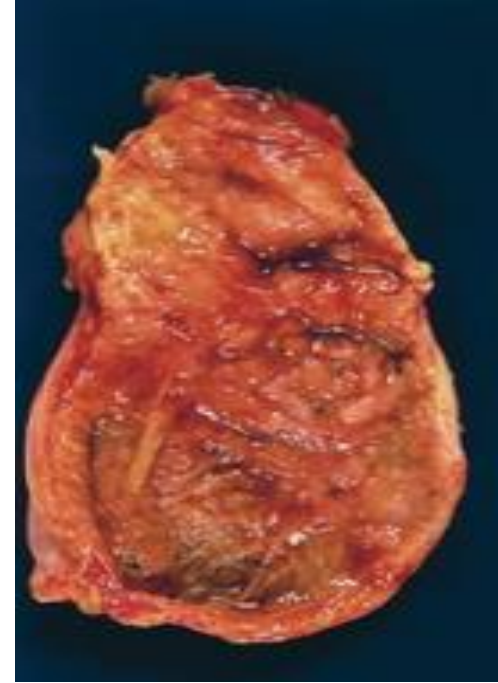
Chronic Cholecystitis: Complications

- Gangrene
- Gallbladder rupture
- Cancer of the gallbladder (rare)
- Jaundice, Pancreatitis, Empyema
- Fistula formation and gallstone ileus
- Rokitansky-Aschoff sinuses
(pseudodiverticula or pockets in the wall of the gallbladder)
- Worsening of the condition.



Chronic Cholecystitis: Red flags for people

- Fever
- Anorexia, weight loss
- Pain that awakens patient
- Blood in stool or urine
- Jaundice
- Edema
- Abdominal mass or organomegaly.



Chronic Cholecystitis: Diagnosis 1

- Leukocytosis with a left shift may be observed
- ALT, AST may be elevated
- Bilirubin and alkaline phosphatase assays may reveal evidence of CBD obstruction
- Amylase/lipase assays are used to assess for pancreatitis; amylase may also be mildly elevated in cholecystitis

Chronic Cholecystitis: Diagnosis 2

- Alkaline phosphatase level may be elevated (25% of patients with cholecystitis)
- Urinalysis is used to rule out pyelonephritis and renal calculi
- All females of childbearing age should undergo pregnancy testing
- Radiography, ultrasonography, CT, MRI, hepatobiliary scintigraphy, ERCP.

US MLE TEST

A 43-year-old woman presents with right upper quadrant pain. She has always had intermittent pain in the same area after certain meals, but her symptoms have never been this persistent before. Vital signs are temperature 38.2 degrees Celcius, heart rate 97, blood pressure 137/84, respiratory rate 14, and oxygen saturation 99% on room air. Body mass index is 29.1. Physical examination reveals tenderness to palpation of the right upper quadrant. What is the recommended imaging study?

1. CT abdomen with oral and IV contrast, 2. CT abdomen with IV contrast only, 3. PET scan, 4. Abdominal ultrasound, 5. Abdominal X-ray.

US MLE TEST EXPLANATION

The correct answer is 4. This patient presents with acute cholecystitis. The most useful imaging study to confirm the diagnosis is a right upper quadrant ultrasound.

Incorrect Answers:

1: Computed tomography of the abdomen exposes the patient to radiation and is not indicated in the diagnosis of acute cholecystitis, 2: Computed tomography of the abdomen exposes the patient to radiation and is not indicated in the diagnosis of acute cholecystitis, 3: Positron emission tomography is useful in diagnosis and staging of cancer but would not be helpful in diagnosing acute cholecystitis, 5: Abdominal X-ray would not help to diagnose acute cholecystitis but could be helpful in the diagnosis of a small bowel obstruction for instance.

Chronic Cholecystitis: Management 1

- Treatment depends on the severity of the condition and the presence or absence of complications
- The following medications may be useful:
- Levofloxacin and metronidazole for prophylactic antibiotic coverage against the most common organisms
- Antiemetics (e.g., promethazine or prochlorperazine) to control nausea and prevent fluid and electrolyte disorders

Chronic Cholecystitis: Management 2

- Analgesics (e.g., oxycodone/acetaminophen)
- Surgical and interventional procedures:
laparoscopic cholecystectomy (standard of care for surgical treatment), percutaneous drainage, ERCP, endoscopic ultrasound-guided transmural cholecystostomy, endoscopic gallbladder drainage.

Chronic Cholecystitis: Prognosis

- The prognosis of chronic cholecystitis is generally good with prompt and effective treatment
- The condition rarely leads to death, and serious complications are also rare
- Cholecystectomy is a common surgical procedure having a very low risk

Chronic Cholecystitis: Prophylaxis

- Chronic cholecystitis is not always preventable
- Eating less fatty foods, controlling weight, and avoiding the risk factors, may relieve symptoms
- A removal of gallbladder (cholecystectomy) and gallstones, will prevent further attacks.

Functional Biliary Disorders:

Plan of the Lecture



- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Functional Biliary Disorders: Definition

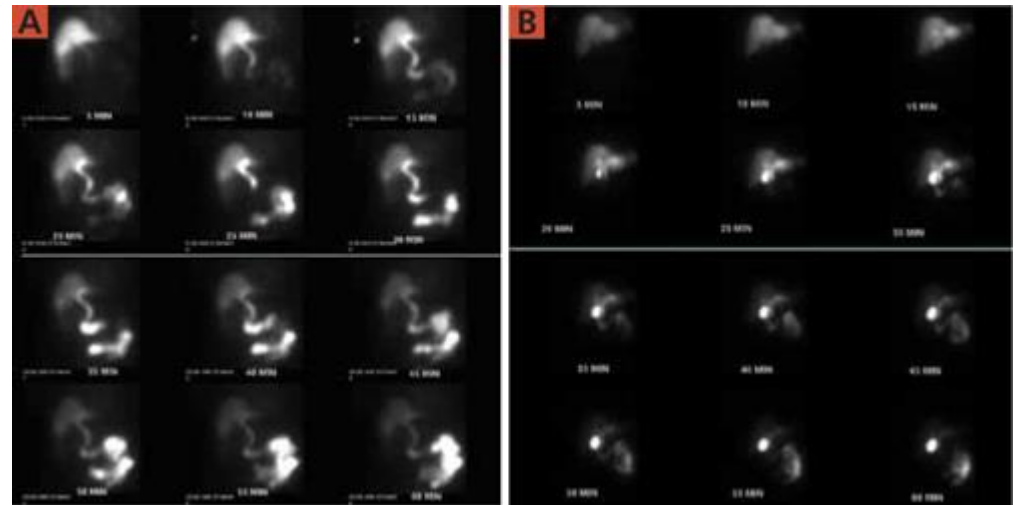
- Functional Biliary Disorders include functional gallbladder disorder (gallbladder dyskinesia, gallbladder spasm, acalculous biliary disease, chronic acalculous gallbladder dysfunction, and cystic duct syndrome) and sphincter of Oddi dysfunction, and are defined as biliary pain resulting from a primary gallbladder and sphincter of Oddi motility disturbances in the absence of gallstones, sludge, microlithiasis, or microcrystal disease
- The diagnosis is considered in patients with typical biliary-type pain who have had other causes for the pain excluded.

Functional Biliary Disorders: Epidemiology

The prevalence of functional gallbladder disorder and sphincter of Oddi dysfunction among patients with biliary-type pain and a normal transabdominal gallbladder ultrasound is up to 8 percent in men and 21 percent in women.

Functional Biliary Disorders: Risk Factors and Etiology

The etiology of functional biliary disorder is unclear, but it is generally regarded as a motility disorder of the gallbladder and sphincter of Oddi.



A hepatobiliary scan: A) normal;
B) functional biliary disorder.

Functional Biliary Disorders: Mechanisms 1

- Functional biliary disorders may result from an initial metabolic disorder (i.e., bile supersaturated with cholesterol) or a primary motility disorder in the absence, at least initially, of any abnormalities of bile composition
- It has been noted that patients with functional gallbladder disorder may have abnormal gastric emptying and colonic transit, suggesting a possible generalized gastrointestinal motility disorder
- The hypothesis that functional gallbladder disorder is related to abnormal gallbladder motility is the basis for measuring the gallbladder ejection fraction as part of the evaluation.

Functional Biliary Disorders:

Clinical Classification

- Gall bladder dysfunction
- Sphincter of Oddi dysfunction



Sphincter of Oddi dysfunction: a dilated bile duct, with progressive narrowing in the terminal (intrapancreatic part), without stones or sludge; vascular structures (hepatic artery and portal vein) were clearly delineated by color Doppler sonography.

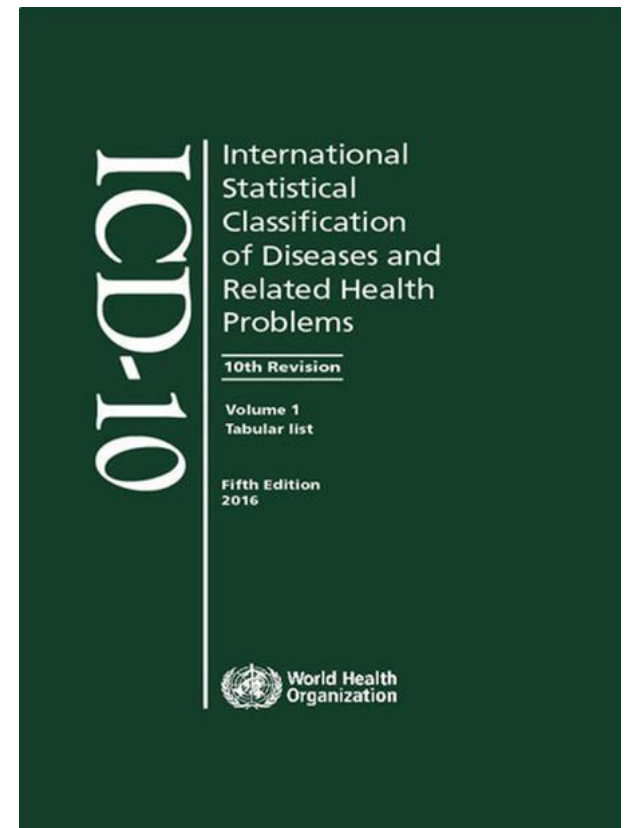
Functional Biliary Disorders:

International Classification of Diseases (ICD)

XI Diseases of the digestive system

K82.8 Other specified diseases of gallbladder (Dyskinesia of cystic duct or gallbladder)

K83.9 Disease of biliary tract, unspecified



Functional Biliary Disorders: Signs and Symptoms 1

- Patients with functional biliary disorder present with biliary-type pain, also known as biliary colic
- The pain is located in the right upper quadrant or epigastrium that may radiate to the back (particularly the right shoulder blade)
- Despite the name, biliary colic is usually constant and not colicky
- The pain plateaus in less than an hour, ranging from moderate to excruciating in severity
- Once it has plateaued, the pain typically lasts at least 30 minutes and then slowly subsides over several hours, with the entire attack usually lasting less than six hours
- The pain is often associated with diaphoresis, nausea, and vomiting

Functional Biliary Disorders: Signs and Symptoms 2

- While biliary-type pain often develops one to two hours after ingestion of a fatty meal, an association with meals is not universal, and in a significant proportion of patients the pain is nocturnal, with a peak occurrence around midnight
- In most cases, the pain has a characteristic pattern and timing for an individual patient
- While the pain is recurrent, it occurs at variable intervals (not daily)
- After an attack, the physical examination is usually normal, with the possible exception of residual upper abdominal tenderness
- While nonspecific dyspeptic symptoms, such as indigestion, abdominal bloating, and belching, may coexist in patients with biliary colic, they are not usually relieved by cholecystectomy.

Functional Biliary Disorders:

Laboratory, Imaging, and Endoscopic Studies 1

- Patients with functional biliary disorder have normal blood tests, including aminotransferases, bilirubin, alkalinephosphatase/gamma-glutamyl transpeptidase, amylase, and lipase
- In addition, abdominal imaging is normal, with no evidence of gallstones, gallbladder sludge, or cholesterol polyps

Functional Biliary Disorders:

Laboratory, Imaging, and Endoscopic Studies 2

- Finally, patients have normal upper endoscopic examinations
- When noninvasive investigations and endoscopic retrograde cholangiopancreatography show no structural abnormality, manometry of both biliary and pancreatic sphincter may be considered.

Functional Biliary Disorders: Diagnosis 1

- Functional biliary disorder is a diagnosis of exclusion in a patient with typical biliary-type pain
- The first step in the evaluation of such patients is to exclude other causes for the patient's pain
- If no other causes are identified, patients should undergo cholecystokinin (CCK)-stimulated cholescintigraphy to confirm the diagnosis

Functional Biliary Disorders: Diagnosis 2

- CCK-stimulated cholescintigraphy allows for calculation of the gallbladder ejection fraction (GBEF), which is low in patients with functional gallbladder disorder (<40 percent) and helps predict which patients are likely to respond to cholecystectomy.

Functional Biliary Disorders: Diagnosis

The Rome IV Criteria 1

- Rome IV criteria require: biliary pain, absence of gallstones or other structural pathology,
- In addition, the criteria that are supportive of functional gallbladder disorder, but are not required, include: low ejection fraction on scintigraphy; normal liver enzymes, conjugated bilirubin, and amylase/lipase

Functional Biliary Disorders: Diagnosis

The Rome IV Criteria 2

- To fulfill the criteria for biliary-type pain, patients need to have pain that: is located in the epigastrium and/or right upper quadrant, occurs at variable intervals (not daily), lasts at least 30 minutes, builds up to a steady level, is severe enough to interrupt daily activities or lead to an emergency department visit, is not significantly (<20 percent) relieved by bowel movements, postural changes, or acid suppression.

Functional Biliary Disorders:

Management: Surgery 1

- Cholecystectomy is the treatment for functional gallbladder disorder
- Patients are candidates for cholecystectomy if they fulfill the clinical criteria for functional gallbladder disorder, if alternative explanations for their symptoms have been excluded, and if their gallbladder ejection fraction (GBEF) is reduced (<40 percent)

Functional Biliary Disorders:

Management: Surgery 2

- Patients who develop pain during cholecystokinin infusion may be particularly likely to respond well to cholecystectomy
- Endoscopic sphincterotomy is the most widely used therapeutic procedure for patients with biliary-type sphincter of Oddi (SO) dysfunction.

Functional Biliary Disorders: Management: Therapeutic Agents 1

- Some therapeutic agents have potential but there is limited evidence for their therapeutic usefulness
- Hormones such as CCK and glucagon can transiently reduce SO tone
- Calcium channel blockers (nifedipine at 10–20 mg p.o.) decreases the SO pressure and lessens phasic contractions in biliary dyskinesia

Functional Biliary Disorders: Management: Therapeutic Agents 2

- Nitrates decrease sphincteric pressure and can alleviate the symptoms, at least in the short term
- Botulinum toxin, when injected into the sphincter reduces its pressure, improves bile flow, and provides some symptomatic relief
- Such medical therapies have several drawbacks; responses tend to be transient and long term reports are lacking.

Functional Biliary Disorders: Prognosis and Prophylaxis

- Functional biliary disorders can cause significant clinical symptoms but are not likely to explain many instances of biliary pain
- Clearly, elucidation of the basis for such dysmotility and the detection of a putative hypersensitive biliary tract should sharpen diagnostic tools, expand therapeutic options, and benefit those with this disabling problem.

Abbreviations

ALT- alanine aminotransferase
AST- aspartate aminotransferase
CBD - common bile duct
CT – computed tomography
HIDA - hepatobiliary iminodiacetic acid scan
EUS - endoscopic ultrasound
INR –international normalized ratio
GBEF - gallbladder ejection fraction
HDL - high-density lipoprotein
MRCP - magnetic resonance cholangiopancreatography

NSAIDs – nonsteroidal anti-inflammatory drugs
RUQ - right upper quadrant
SO - sphincter of Oddi
TPN - long-term total parenteral nutrition
XGC - xanthogranulomatous cholecystitis
UDCA - ursodeoxycholic acid RBCs - red blood cells
PT – prothrombin index
ERCP - endoscopic retrograde cholangiopancreatography
CCK - cholecystokinin

Diagnostic and Treatment Guidelines

[Asymptomatic Gallstone Disease](#)

[Biliary Dyspepsia: Functional Gallbladder and Sphincter of Oddi Disorders](#)

[Cholecystitis](#)

[Cholecystitis Treatment & Management](#)

[Chronic acalculous cholecystitis: clinical features, diagnosis and treatment](#)

[Diagnosis and management of gallstone disease: summary of NICE guidance](#)

[Gallstones \(Cholelithiasis\) Treatment & Management](#)

[Prevention, diagnosis and treatment of gallstones](#)