

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



11.	Chronic disease of the small intestine	2	15/11
12.	Chronic disease of the colon: IBS and nonspecific colitis	2	22/11
13.	Chronic pancreatitis	2	29/11
14.	Chronic hepatitis	2	06/12
15.	Cirrhosis of the liver	2	13/12

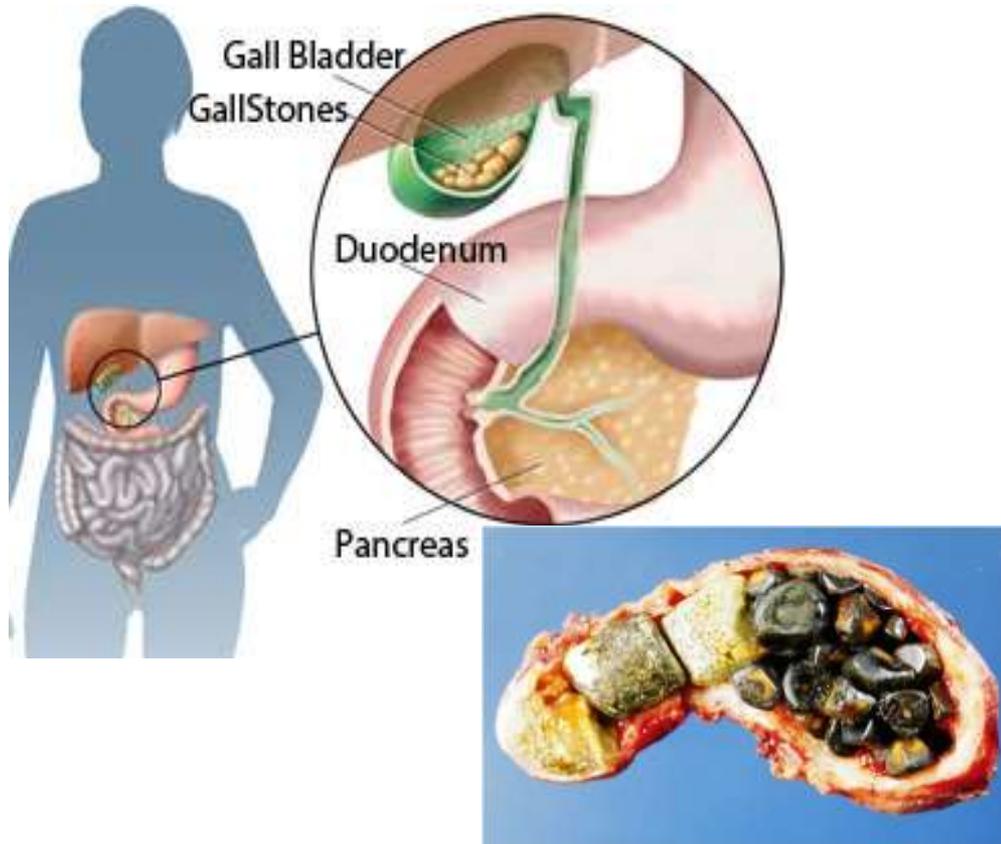
Supportive module 2: Basics of diagnosis, treatment and prevention of major gastroenterological diseases

# 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, N. Makienko  
V.N. Karazin National University Medical School' Internal Medicine Dept.

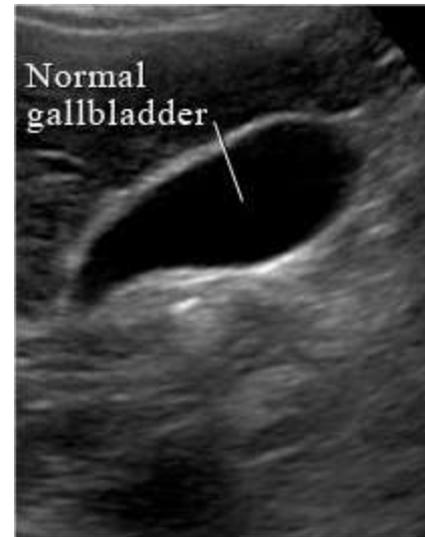
# Cholelithiasis: Plan of the Lecture



- 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.



# Cholelithiasis: Epidemiology

- 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
- 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

- 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
- 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

- 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
- 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

- 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)
- 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

- 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
- 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

- 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
- 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

- 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.

# 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

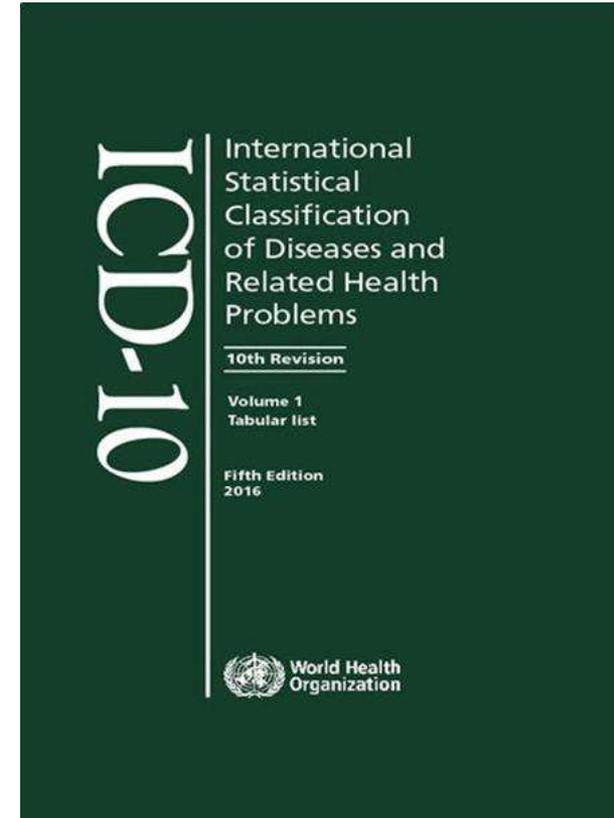
K80.2 Calculus of gallbladder without cholecystitis

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

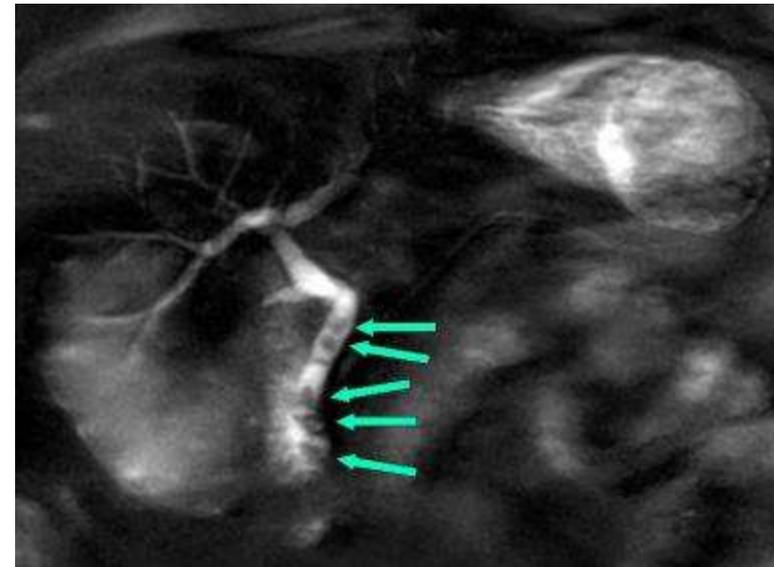
- Cholesterol gallstones: the most common type of gallstone, called a cholesterol gallstone, often appears yellow in color and are composed mainly of undissolved cholesterol, but may contain other components
- Pigment gallstones: these dark brown or black stones form when bile contains too much bilirubin.



# 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

- 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
- 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

- 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
- 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

- 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)
- 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  $\geq 30$ ), 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

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

# Cholelithiasis: Complications

## Gallbladder Stones

- 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
- 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

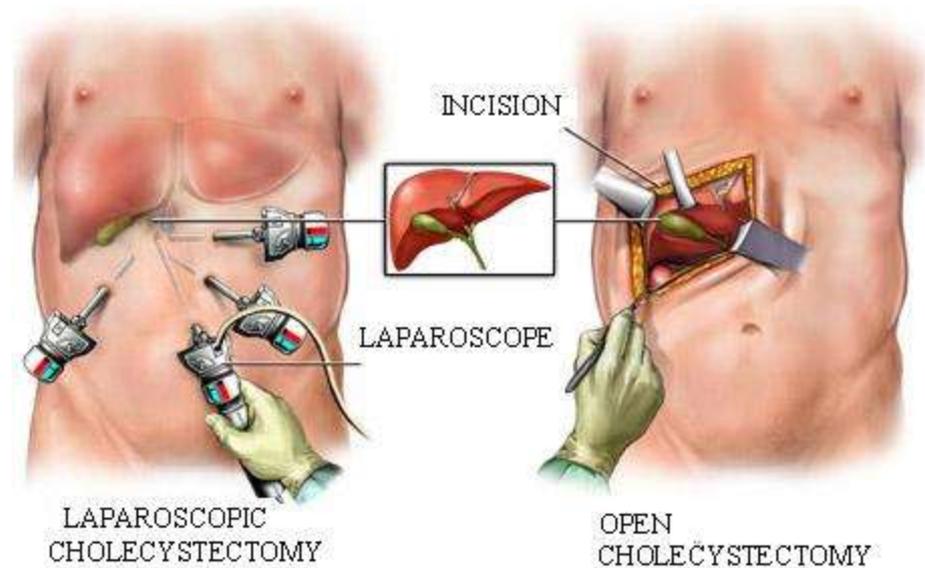
# Cholelithiasis: Complications

## Common Bile Duct Stones

- 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
- 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



# Cholelithiasis: Diagnosis

- 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
- 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

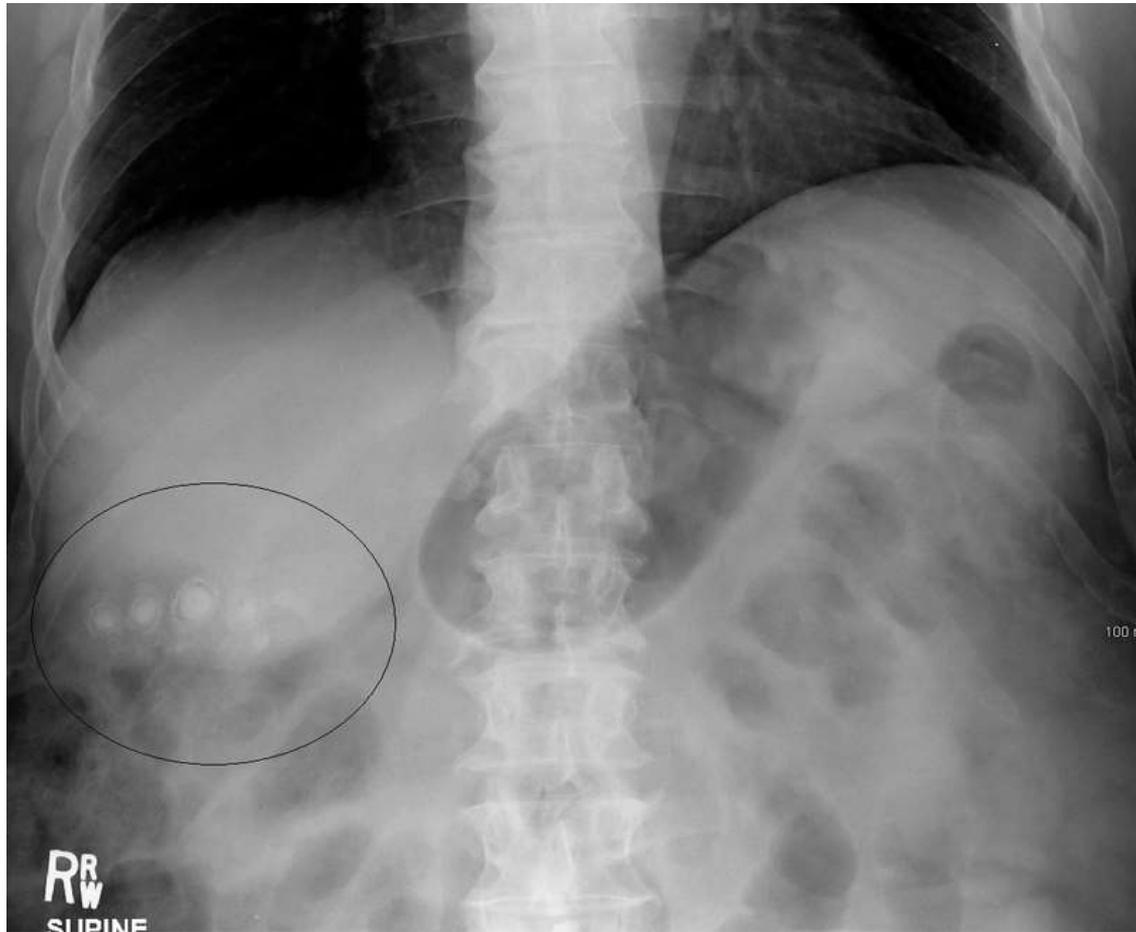
## Transabdominal Ultrasonography



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

# Cholelithiasis: Diagnosis

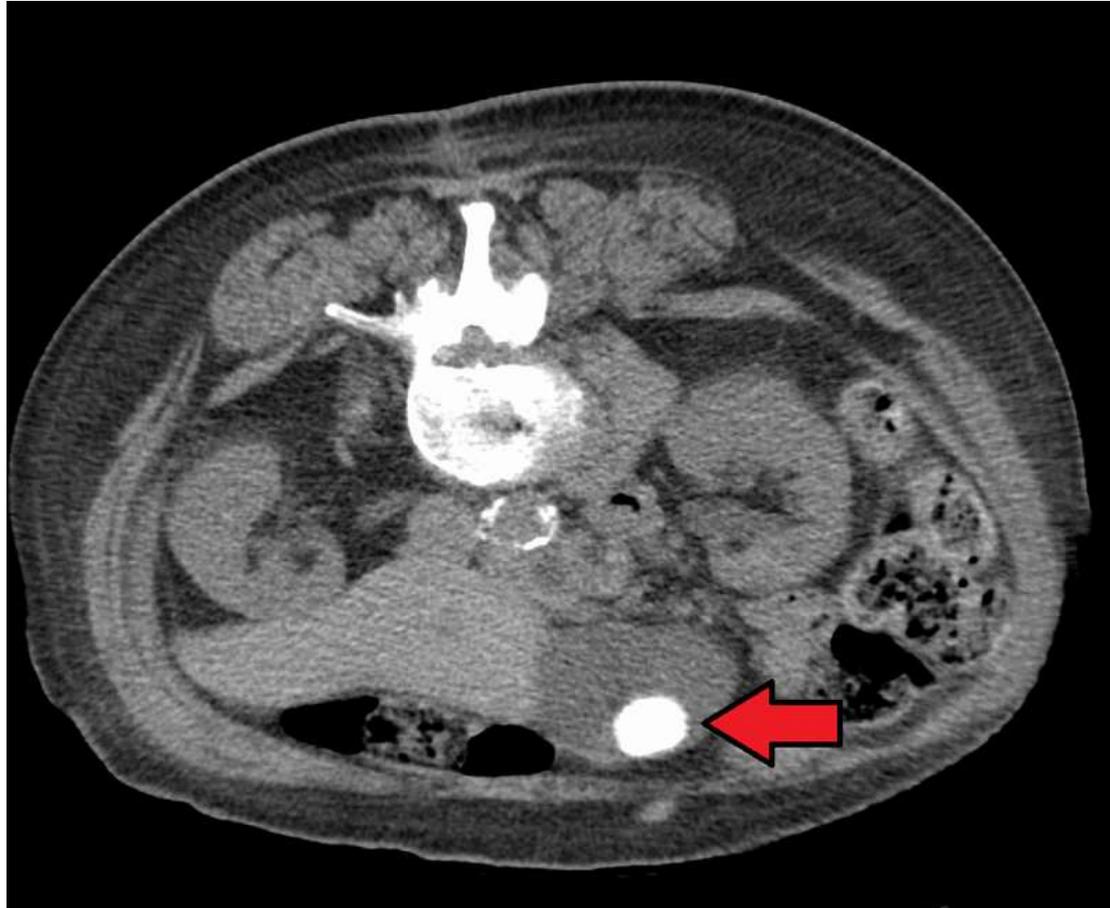
## Plain X-ray



Gallstones.

# Cholelithiasis: Diagnosis

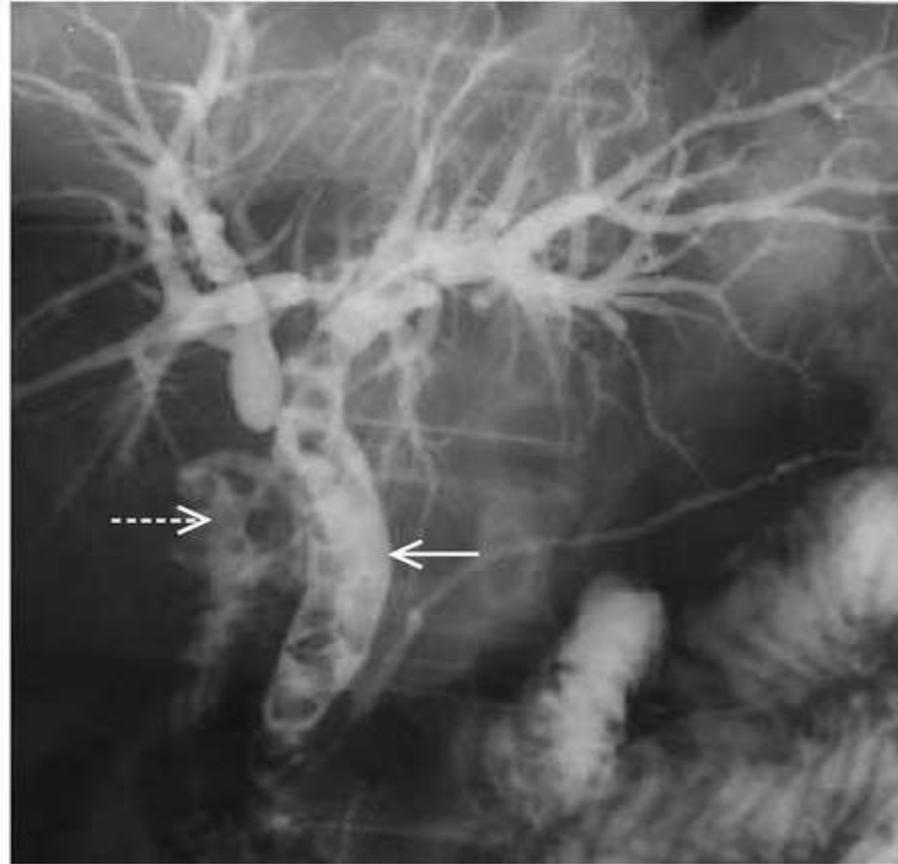
## Computed Tomography



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

- 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
- 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

- 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
- 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

- 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
- 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

- 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
- 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

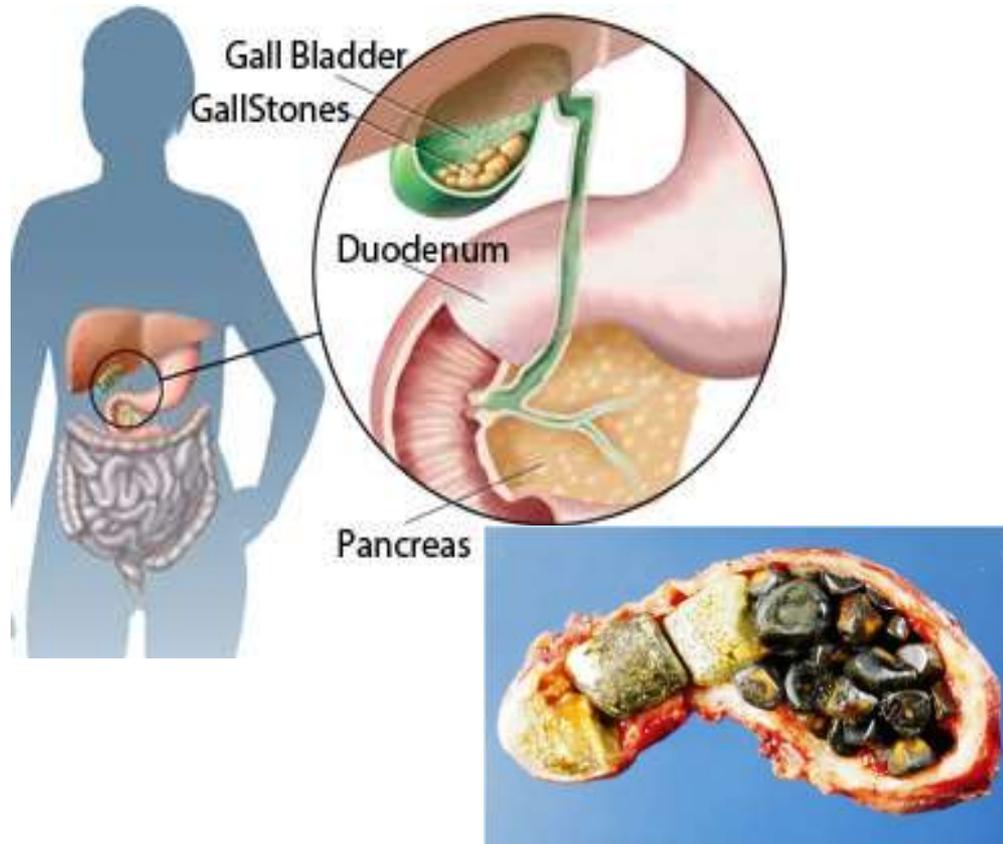
# Cholelithiasis: Prognosis

- 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
- 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 ( $\geq 50$  years) and body mass index (BMI) ( $\geq 30$  kg/m<sup>2</sup>) as independent predictive factors
- Approximately 10-15% of patients have an associated choledocholithiasis.

# Cholelithiasis: Prophylaxis

- 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
- 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

- 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 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.

# 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

- 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
- 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

- 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
- 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

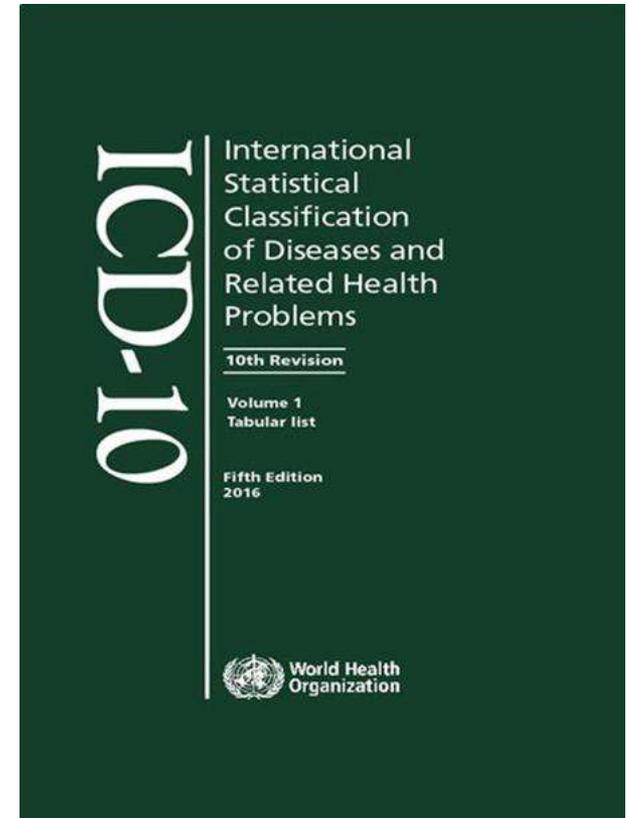
K81 Cholecystitis

K81.0 Acute cholecystitis

K81.1 Chronic cholecystitis

K81.8 Other cholecystitis

K81.9 Cholecystitis, unspecified



# Chronic Cholecystitis: Classification

## Clinical

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)

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

- 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
- 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

- 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
- 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

- 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
- 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

- 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
- 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.

# Chronic Cholecystitis: Management

- 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
- 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

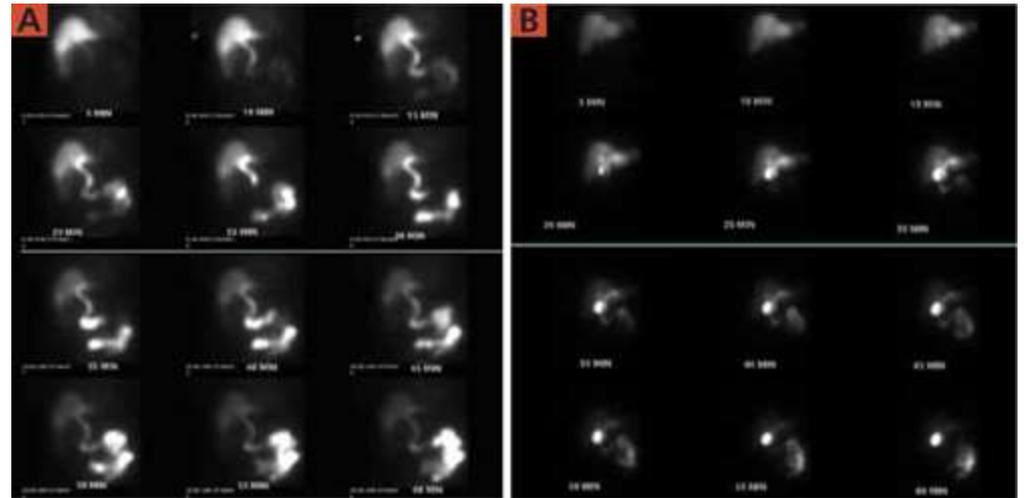
- Functional Biliary Disorders include functional gallbladder disorder (gallbladder dyskinesia, gallbladder spasm, acalculous biliary disease, chronic acalculous gallbladder dysfunction, and cystic duct syndrome) and sphincter of Oddi dysfunction, and are defined as biliary pain resulting from a primary 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

- 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.

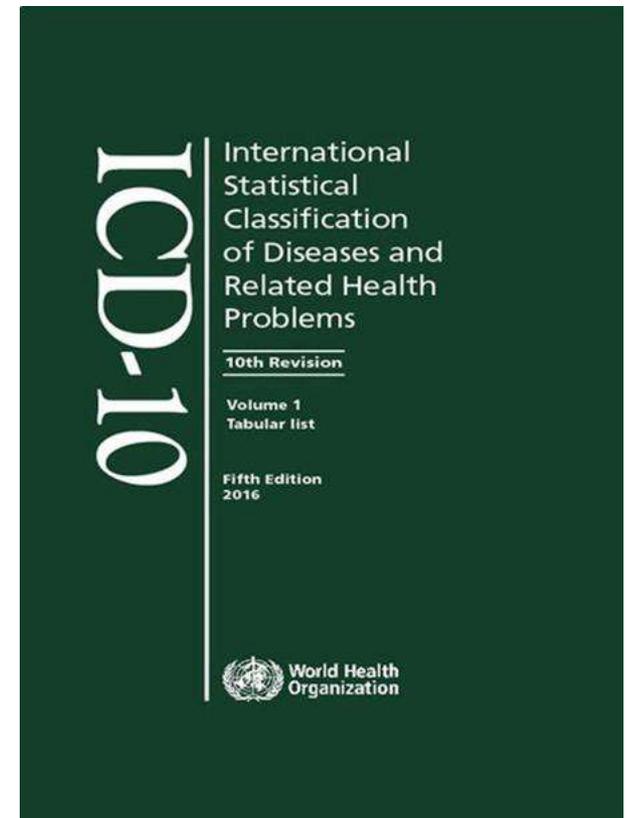
# Functional Biliary Disorders:

## 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

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

- 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 cholecystikinin (CCK)-stimulated cholescintigraphy to confirm the diagnosis
- 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

- 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
- 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

- 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)
- 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

- 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
- 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](#)