

Color index:

Main text (black)

Female Slides (Pink)

Male Slides (Blue)

Important (Red)

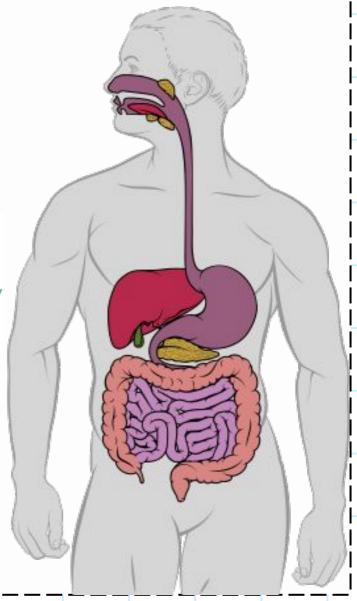
Dr's note (Green)

Extra Info (Grey)













Recognize the predisposing factors of gallstones (Cholelithiasis) and cholecystitis



Describe the pathological features different types of cholecystitis.



Describe the clinical features different types of cholecystitis.



Understand the pathogenesis of acute and chronic cholecystitis



Understand the gallbladder carcinoma.

THIS LECTURE WAS PRESENTED BY DR.WAJD ALTHAGAFI & DR.AHMED ALHUMAIDI



🌟 VERY SPECIAL THANKS FOR AROUB ALMAHMOUD & AISHAH BOUREGGAH FOR THEIR MAGNIFICENT EFFORTS 🜟





IF YOU WANT TO READ THE LECTURE FROM <u>ROBBINS</u>



IF YOU WANT TO READ THE LECTURE FROM FIRST AID

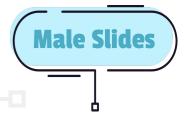


IF YOU WANT TO WATCH <u>OSMOSIS VIDEO</u>



IF YOU WANT TO READ <u>OSMOSIS SUMMARY</u>

Introduction



Bile Contents

Water: 97-98 %

Bile salts: 0.7 %

Bilirubin: 0.2 %

Fats (cholesterol, fatty acids and lecithin):0.51 %

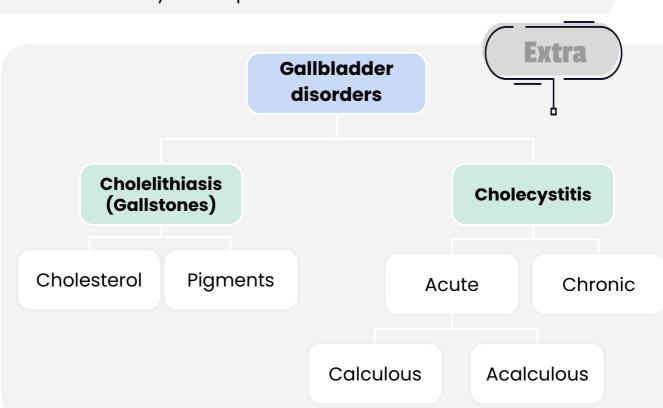
Inorganic salts: 200 meg/L

The two main pigments of bile are

Bilirubin, which is orange-yellow

Biliverdin, which is green

When mixed they are responsible for the brown color of feces.



Cholelithiasis (Gallstones)

Introduction



Affects 10-20% of adults in Western countries in Northern Hemisphere, 20-40% in Latin American countries & only 3-4% in Asian countries.

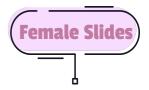


Majority of gallstones (>80%) are "silent/asymptomatic" and most individuals remain free of biliary pain or stone complications for decades. Usually the symptoms appear after the movement of stones into Common bile duct.

Types

	Cholesterol Stones	Pigment Stones	
Definition	Contain crystalline cholesterol monohydrate (80%).	Made of bilirubin calcium salts (20%).	
Risk Factors	 □ Demography: Northern Europe, North and South America, Native Americans, Mexican Americans. □ Advancing age. □ Female sex hormones: → Female gender. → Oral contraceptives. → Pregnancy. □ Obesity and insulin resistance. □ Rapid weight reduction. □ Gallbladder stasis. □ Inborn disorders of bile acid metabolism. □ Hyperlipidemia/Dyslipidemia syndromes. 	 Demography: Asian more than Western, rural more than urban. Chronic hemolysis/Hemolytic syndromes (e.g., sickle cell anemia, hereditary spherocytosis). Biliary infection. Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency. 	
Pic	CM1 2 3 4 5 6 7 8 9 10		

Cholelithiasis (Gallstones)



Prevalence



- Prevalence increases throughout life especially above age of 40.
- The prevalence in women of all ages is about twice as high as in men.



 Prevalence approaches 50% to 75% in certain Native American populations (Pima, Hopi, and Navajo), seems to be related to biliary cholesterol hypersecretion.



 A positive family history imparts increased risk, associated with impaired bile salt synthesis and secretion.

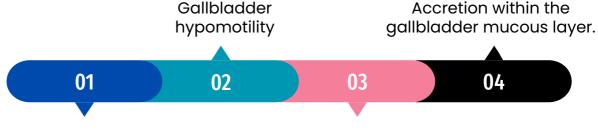


- Estrogens increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol. (oral contraceptive use and with pregnancy).
- Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent are strongly associated with increased biliary cholesterol secretion.



 Any condition in which gallbladder motility is reduced predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury.

contributing factors



Supersaturation

Crystal nucleation

ALL TEXT IN FEMALES SLIDES BUT MALES DR EXPLAINED IT ON THE PICTURE (IN BOTH)

Cholesterol Gallstones



Cholesterol Gallstones

Pigment Gallstones

Pathogenesis

Bile formation is the only significant pathway for elimination of excess cholesterol from the body; either as free cholesterol or as bile salts.

Cholesterol is water insoluble; so it binds to bile salts & lecithins in the bile.

Cholesterol gallstone formation involves three simultaneous defects:







Female Slides

Supersaturation of bile with cholesterol

the result of hepatocellular hypersecretion of cholesterol.

Gallbladder hypomotility

It promotes nucleation typically around a calcium salt crystal nidus.

Mucus hypersecretion in the gallbladder

This traps the crystals, permitting their aggregation into stones.

hypersecretion of cholesterol -> cholesterol concentrations exceed the solubilizing capacity of bile

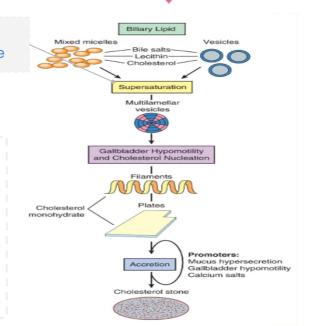
Deep Focus Question



What word BEST describes the process by which gallstones are formed?

- A. Supersaturation
- B. Saponification
- C. Emulsification
- D. Lamellation
- E. Crystallization

Answer: A



Cholesterol Gallstones



2

Cholesterol Gallstones

Pigment Gallstones

Morphology









Pale yellow, round to ovoid, and have a finely granular, hard external surface.



Stones composed largely of cholesterol are radiolucent.



Sufficient calcium carbonate is found in only 10% to 20% of cholesterol stones to render them radiopaque.

Cholesterolosis

Cholesterolosis, also known as adenomyomatosis, is a condition where the gallbladder's inner lining becomes thickened due to the accumulation of cholesterol and other fatty substances in small pockets within its wall.

Cholesterol hypersecretion by the liver promotes excessive accumulation of cholesterol esters within the lamina propria of the gallbladder.

The mucosal surface is studded with minute yellow flecks, producing the "strawberry gallbladder".







Pigment Gallstones

Cholesterol Gallstones

Pigment Gallstones

Pathogenesis

Pigment stones form when the bile contains a high concentration of unconjugated bilirubin – poorly soluble in water – in the biliary tree, as may occur in patients with **chronic** extravascular red cell **hemolysis** or with certain infections of the biliary tract, such as liver flukes "Opisthorchis sinensis", E. Coli, and Ascaris lumbricoides.

The precipitates are primarily insoluble calcium bilirubinate salts.

Morphology

Pigment gallstones are usually black and/or brown.

1

Black stones found in sterile gallbladder while Brown stones found in infected intrahepatic or extrahepatic bile ducts. 2

Both are soft and usually multiple.

3

Brown stone are greasy.



Because of calcium carbonates and phosphates, approximately 50% to 75% of black stones are radiopaque.

Deep Focus Question



Pigment gallstones are most likely in which of the following forms of alpha thalassaemia?

- A. Hemoglobin Barts disease
- B. Alpha thalassemia trait (cis pattern)
- C. Silent carrier of alpha thalassemia
- D. Alpha thalassemia trait (trans pattern)
- E. Hemoglobin H disease

Answer: E



Cholesterol & Pigment Gallstones



Clinical Features



70% to 80% of patients remain asymptomatic.



Symptoms:

- → Spasmodic or "colicky" right upper quadrant pain, which tends to be excruciating.
- → It is usually due to obstruction of bile ducts by passing stones.



Complications:

- → Empyema
- → Perforation
- → Fistula
- → Cholangitis: Inflammation of the biliary tree.
- → Obstructive cholestasis
- → Pancreatitis
- → Occasionally, a large stone may erode directly into an adjacent loop of small bowel, generating gallstone ileus "intestinal obstruction" (in case the stone is very large it could compress the transverse colon causing obstruction)
- → Most notable is the increased risk for gallbladder carcinoma.
- The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction; it is the very small stones, that are the more dangerous.

Acute Cholecystitis





CHOLECYSTITIS

- o Inflammation of the gallbladder.
- May be acute, chronic, or acute superimposed on chronic.
- o It almost always occurs in association with gallstones.

Overview

- o Acute inflammation of GB that contains stones.
- o Is precipitated in 90% by obstruction of cystic duct or GB neck.
- Is most common major complication of gallstones & most common reason for emergency cholecystectomy.

Pathogenesis Female Slides

1

2

3

4

Obstruction of bile outflow → chemical irritation & inflammation of GB wall.

Phospholipases derived from mucosa →

hydrolyze biliary lecithin to lysolecithin which is toxic to mucosa Disruption of normally protective glycoprotein mucous layer → exposes mucosal epithelium to detergent action of bile salts

PGs released
within distended
GB wall→ enhance
mucosal & mural
inflammation →
Distention & ↑
intraluminal
pressure →
compromise blood
flow to mucosa.

Acute Cholecystitis

Acute calculous Cholecystitis

+ Gross morphology

Enlarged and tense, and bright red to green-black.: gangrenous

Serosa is frequently covered by fibrin or fibrinopurulent exudate (empyema), and hemorrhage.

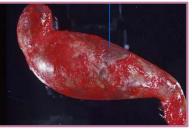
The lumen is filled with a cloudy or pure pus "empyema".

The wall is thickened, oedematous, and hyperemic.

Transformed into a green-black necrotic "gangrenous cholecystitis"

No histological differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the former







+(Clinical Features

01evere/Progr

Severe/Progressi
ve, usually
constant right
upper quadrant
or epigastric
pain/abdominal
pain, radiating
to right
shoulder.

02

Mild fever, nausea, leukocytosis & prostration are classic 03

RUQ tenderness & rigidity 04

Conjugated hyperbilirubin emia " if CBD is obstructed

05

Mild attacks
usually
subside
spontaneousl
y within 1-10
days

06

Recurrence is common

07

~ 25% are ill enough → emergency surgery 08

May appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical intervention.

Acute Cholecystitis

Acute Acalculous Cholecystitis



- More insidious, since symptoms are obscured by the underlying conditions precipitating the attacks.
- A higher proportion of patients have no symptoms referable to the gallbladder.
- The incidence of gangrene and perforation is much higher than in calculous cholecystitis.
- No stones found in 5-12% of GBs removed for acute cholecystitis.

+ Etiology



Following major surgery (Postoperative)



Multisystem organ failure



Severe bruns



Severe trauma



The postpartum state



Sepsis

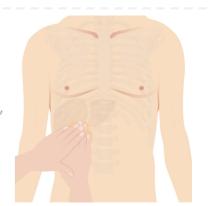


Other contributing factors: dehydration, GB stasis & sludging, vascular compromise, and bacterial contamination



Clinical Note

Patient with Cholecystitis present with **Positive Murphy's sign** Examiner places hand on the gallbladder area (right subcostal area). Patient is instructed to take a deep breath. On inspiration, the inflamed gallbladder descends, coming in contact with the examiner's hand and causing pain.



Chronic Cholecystitis



Overview



Chronic cholecystitis may be a sequel to repeated bouts of mild to severe acute cholecystitis, but in many instances, it develops in the apparent absence of antecedent attacks. Usually no history of previous acute attacks



It is associated with cholelithiasis in over 90% of cases. Obstruction of GB outflow by stones is NOT a requisite, The Causes is Due to supersaturation of bile.



Microorganisms can be cultured from bile in the only 1/3 of cases;mainly E. coli and enterococci

Clinical features

The symptoms of calculous chronic cholecystitis are similar to those of the acute form and range from biliary colic to indolent recurrent attacks of right upper quadrant pain and/or steady epigastric distress.

Patients often have intolerance to fatty food, belching and postprandial epigastric distress, sometimes include nausea and vomiting.



Gross Morphology

The morphologic changes are extremely variable and sometimes minimal.
Gall bladder may be:
1.Contracted (fibrosis)
2. Small or normal in size
3. enlarged (from obstruction)

2

The wall is variably thickened "Fibrosis"

Almost always contains stones.

Chronic Cholecystitis

Histopathologic Morphology









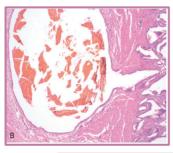
Chronic
inflammation in
the wall with
submucosal &
subserosal
fibrosis

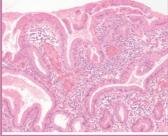
Xanthogranuloma tous cholecystitis abundant lipid filled macrophages Prominent

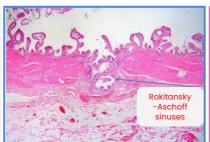
Rokitansky-Asc
hoff sinus

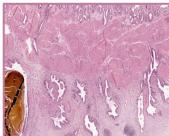
"outpouchings of
mucosal
epithelium
through GB wall"

Lymphocytic infiltration









+ (Complications



Bacterial superinfection $\rightarrow\,$ cholangitis or sepsis



Gallbladder perforation → local abscess



Gallbladder rupture → diffuse peritonitis



Biliary enteric fistula → entry of air and bacteria into biliary tree with drainage of bile into adjacent organs, and potentially gallstone-induced intestinal obstruction (ileus)



Aggravation of pre-existing medical illness -> cardiac, pulmonary, renal, or liver decompensation

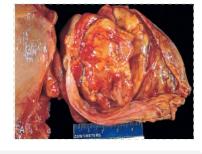


Gallbladder Carcinoma

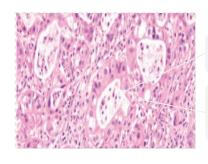
Female Slides

Osmosis Vid

Gallbladder carcinoma			
Overview	 Most common malignant tumor of the extrahepatic biliary tract Mainly in 7th decade of life Slightly more common in women Usually discovered late "unresectable" mean 5 - year. survival rate is 5-12% 		
Risk factors	 Gallstones (found in 95% of the cases) Infections of the biliary tree. If both of the first two occurred = Chronic inflammation Primary sclerosing cholangitis 		
Gross patterns	 Exophytic: Irregular, cauliflower-like mass growing into lumen & invading the underlying wall at same time 		
of growth	 Infiltrating: More common pattern of growth Poorly defined area diffuse wall thickening & induration 		
Microscopically	 Most are adenocarcinomas 5% Squamous cell carcinoma or adenosquamous 		
Clinical features	 Cancer is usually discovered at time of surgery for stone Similar to gallstones: insidious abdominal pain, jaundice, anorexia, nausea & vomiting Only 10% are discovered early at a resectable stage, usually presents at advanced stage 		



Fragmenting mass



Glands

Lined with Malignant cells

Well differentiated

Keywords

•		
cholelithiasis	Cholesterol stones	 Dyslipidemia & Obesity, insulin resistance Gallbladder stasis Female sex hormones (Female gender, Pregnancy and Oral contraceptives) Supersaturation of bile with cholesterol Gallbladder hypomotility Mucus hypersecretion pale yellow stone Stones composed of largely of cholesterol: radiolucent Stones with sufficient calcium carbonate: radio- opaque.
	Pigment stones	 Chronic haemolysis eg: hemolytic anemia Biliary infection: E.coli, Ascaris lumbricoides liver fluke Opisthorchis sinensis lleal disease cystic fibrosis biliary tract of unconjugated bilirubin calcium bilirubin salts. black and/or brown stone black stones: radiopaque
	Cholesterolosis	 excessive accumulation of cholesterol esters within the lamina propria of the gallbladder strawberry gallbladder
Cholecystitis	Acute Cholecystitis	 contains stones. (Chronic & Acute) Right upper quadrant pain, often radiating to right shoulder. Fever bright red to green-black. empyema Transformed into a green-black necrotic "gangrenous cholecystitis" acalculous: No stones due to Postoperative, trauma, burns, organ failure, Sepsis, postpartum state
	Chronic cholecystitis	 associated with cholelithiasis normal in size or enlarged Thickened wall contracted "fibrosis". Xanthogranulomatous cholecystitis Prominent Rokitansky-Aschoff sinus Patients often have intolerance to fatty food
Gallbladder Carcinoma	 due to Gallstones or Infections of the biliary tree or Primary sclerosing cholangitis Exophytic: cauliflower-like mass Infiltrating: Poorly defined area of diffuse wall thickening & induration 	



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Which type of gallstones are predominantly composed of bilirubin calcium salts?

A- Cholesterol stones

B- Pigment stones

C- Calcium stones

D- Bile salt stones

What is the main cause of pigment stones?

A- Supersaturation of bile with cholesterol

B- Gallbladder hypomotility

C- Chronic hemolytic conditions

D- Excessive bile salt secretion

Which type of gallstone is radiolucent?

A- Cholesterol stones

B- Pigment stones

C- Calcium stones

D- Bile salt stones

What is the precipitating factor for acute calculous cholecystitis in most cases?

A- Biliary infection

B- Gallstone obstruction

C- Chronic hemolysis

D- Bile duct blockage





What can be a possible complication of acute cholecystitis?

A- Cirrhosis

B- Pancreatitis

C- Lung cancer

D- Arthritis

Which enzymes derived from the gallbladder mucosa contribute to acute cholecystitis?

A- Phospholipases

B-Lipases

C- Amylases

D-lactase

Which of the following causes acute acalculous cholecystitis?

A- Kidney stones

B- Sepsis

C- Ileum resection

D- Hemolytic anemia

In cholesterolosis, which one of the following is the cause of "spasmodic pain" in this condition?

A-Inflammation

B- Pancreatitis

C- Passing the stones into the common bile duct

D- Infection





1. A 40-year-old black woman has frequent indigestion after meals and abdominal pain. Physical examination demonstrates a moderately obese woman in no acute distress. An ultrasound examination demonstrates numerous echogenic objects within the gallbladder. A cholecystectomy is performed, and the surgical specimen is shown in the image. The gallstones seen in this patient are typically associated with which of the following diseases?

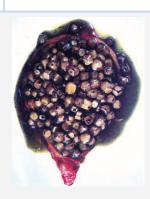


A.Chronic pancreatitis

B.Diabetes mellitus

C.Familial hypercholesterole mia D.Sickle cell disease

2.A 47-year-old woman presents with a 3-month history of vague upper abdominal pain after fatty meals, some abdominal distension, and frequent indigestion. Physical examination shows an obese woman (BMI = 30 kg/m2) with right upper quadrant tenderness. An ultrasound examination discloses multiple echogenic objects in the gallbladder. The opened gallbladder is shown in the image. Which of the following metabolic changes is most likely associated with the formation of gallstones in this patient?



A.Decreased hepatic bilirubin conjugation B.Decreased serum albumin

C.Increased hepatic calcium secretion D.Increased hepatic cholesterol secretion

3.For the patient described in Question 2, which of the following is a common complication?

A.Bile peritonitis

B.Chronic passive congestion of the liver

C.Confluent hepatic necrosis

D.Extrahepatic biliary obstruction

4.A 45-year-old, mildly obese woman presents with a 1-week history of upper abdominal pain, fever, shaking chills, and occasional vomiting. Physical examination shows severe right upper quadrant tenderness. Laboratory studies include serum bilirubin of 1.0 mg/dL, AST of 25 U/L, ALT of 35 U/L, alkaline phosphatase of 220 U/L (high), WBC of 14,000/µL, and amylase of 95 U/L (normal). An ultrasound examination of the abdomen reveals a normal-appearing liver and bile duct and thickening of the wall of the gallbladder. Which of the following is the most likely diagnosis?

A.Acute cholecystitis

B.Acute pancreatitis

C.Adenocarcinoma of the pancreas

D.Primary biliary cirrhosis







EXTRA CASES MAY REQUIRE EXTRA INFO

1.A 37-year-old woman, gravida 5 para 5, is brought to the emergency department due to sudden-onset colicky abdominal pain in the right upper quadrant that started 1 hour ago. She states she has been feeling nauseous for several hours since the pain started and has vomited twice. She has had several episodes of abdominal discomfort in the past, especially after consuming food. Medical history is significant for hypertriglyceridemia and obesity. Medications include fenofibrate. Temperature is 38.0°C (100.4°F), pulse is 75/min, and blood pressure is 135/85 mmHg. BMI is 36 kg/m2. Abdominal examination reveals inspiratory arrest during palpation of the right upper quadrant. An abdominal ultrasound shows a thickened gallbladder wall and exquisite tenderness when the probe is applied on the right upper quadrant. A diagnosis is made, and the patient receives pain medication and IV hydration. Two weeks later, the patient undergoes elective laparoscopic cholecystectomy which reveals multiple stones within the gallbladder. Which of the following is the most likely cause of this patient's condition?

A.Decreased activity of aromatase enzyme

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110

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2000

これには、またいかとうという。

5.00

B.Increased activity of β-glucuronidase enzyme

C.Decreased activity of 7a-hydroxylase enzyme

D.Decreased activity of HMG-CoA reductase enzyme

2.A 65-year-old woman comes to a follow-up appointment following hospitalization due to diverticulitis. Since then, she has been recovering well and has no complaints. Medical history is significant for cholelithiasis, hypercholesterolemia, diverticulitis and constipation. Medications include statins, multivitamins, and supplemental fiber. She does not smoke, drink alcohol, or use illicit drugs. On physical examination, the abdomen is soft and nontender, and bowel sounds are present. A CT obtained at the recent hospitalization is shown:



A.Budd-Chiari syndrome B.Gallbladder adenocarcinoma

C.Hepatocellular carcinoma

D.Liver cirrhosis

3.A 65-year-old man comes to the clinic due to abdominal discomfort, fatigue, and weight loss for the past three months. He states the pain is mainly in the right upper quadrant and describes the pain as vague, 3/10, and constant. He immigrated from Bolivia 2 years ago. Immunizations are up to date. Medical history is significant for hypertension and diabetes mellitus. Vitals are within normal limits. Physical examination reveals an icteric patient. On abdominal examination, pain is produced when pressure is applied to the right subcostal area. An abdominal ultrasound examination shows calcification within the gallbladder. When the patient is asked to lie on his side, the calcifications are observed at the same location. Which of the following is a risk factor for this patient's condition?

A.Gallstone disease

B.Ionizing radiation

C.Clonorchis sinensis infection

D.Hepatitis B infection



Pathology Team

