Lecture 13
Cholecystitis

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- Compare the various types of gallstones, how they are formed, what the risk factors for their development are, and what complications they can cause.
- Recognize the predisposing factors of cholecystitis and the different types of cholecystitis.
- Understand the pathogenesis of acute and chronic cholecystitis

References:

Lecture Slides & Robbins.

General information (you can find theses in physiology and hematology lectures)

A. Bile salts/acids (~67%)

1) Hepatic product of CH metabolism
2) Water soluble
3) Detergent action renders CH soluble in bile.

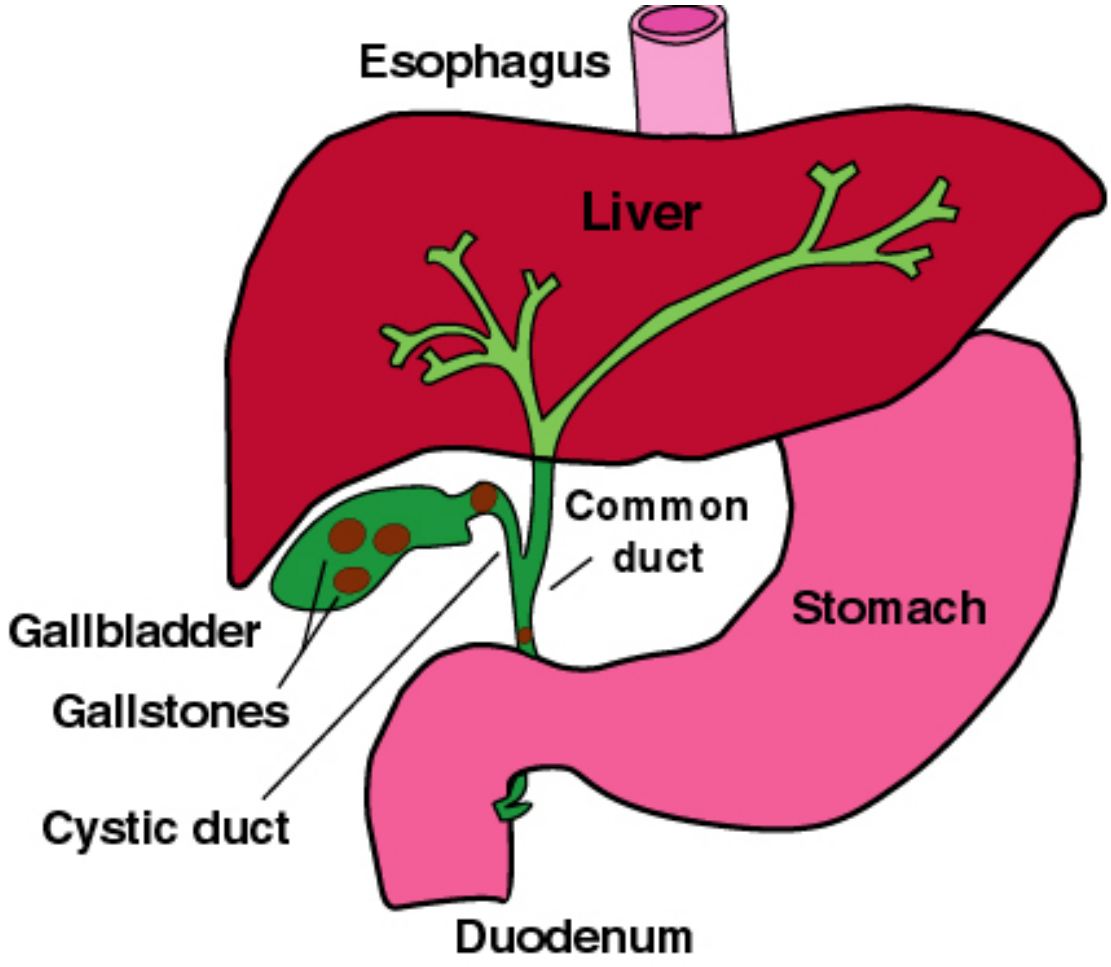
B. Phospholipid (22%)

Mainly lecithin, Hydrophobic, Solubilizes CH in bile

C. Protein (4.5%), free CH (4%), conjugated bilirubin (0.3%)

- In extravascular hemolytic anemia (EHA; e.g., hereditary spherocytosis, sickle cell disease), there is an increase in UCB (unconjugated bilirubin) (macrophage destruction of spherocytes/sickle cells) and a corresponding increase in the uptake and conjugation of UCB to conjugated bilirubin (CB) in the liver. In the gallbladder, some of the CB is converted back to UCB, which combines with calcium to form calcium bilirubinate stones.

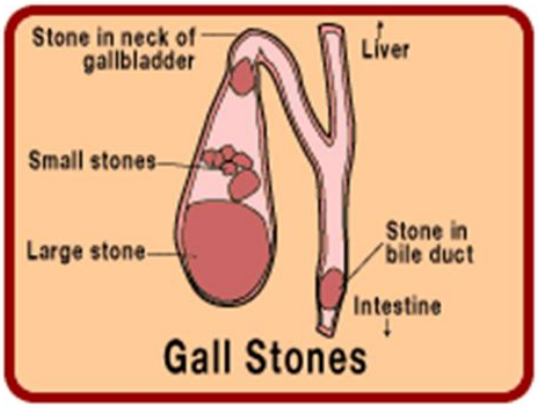
D. Water, electrolytes, bicarbonate



Disorders of the Gallbladder:

Cholelithiasis (Gallstones):

Majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades.



There are two main types of gallstones:

	Cholesterol stones	Pigment stones
Definition	About 80%, containing more than 50% of crystalline cholesterol monohydrate. Note: Cholesterol stones contain calcium, but not as much as pigment stones.  Multiple pale yellow oval cholesterol stone	20%, containing bilirubin calcium salts.  Multiple black pigment stone (black stones indicate sterile gallbladder)
Prevalence and Risk Factors	Demography: northern Europeans, North and South Americans, Native Americans, Mexican Americans (Industrial countries; the people have cholesterol rich diet) ▪ Advancing age ▪ Female gender ▪ Pregnancy ▪ Gallbladder stasis ▪ Female sex hormones ▪ Oral contraceptives ▪ Obesity and metabolic syndrome ▪ Rapid weight reduction ▪ Inborn disorders of bile acid metabolism ▪ Hyperlipidemia syndromes	Demography: Asians more than Westerners, rural more than urban ▪ Chronic hemolytic syndromes ▪ Biliary infection ▪ Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

Cholesterol stones are yellow in color and radiolucent.
Pigment stones are radiopaque.

Always keep in mind that anything related to hormonal imbalance, weight problems or metabolism abnormality, can be a cause of cholesterol stones.

Chronic hemolytic syndromes = increased unconjugated bilirubin level in plasma.
Remember that patients coming from villages are more prone to pigment stones that to cholesterol.

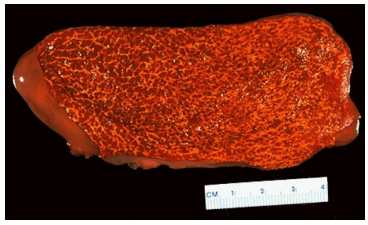
	Cholesterol stones	Pigment stones
Pathogenesis	▪ Cholesterol is rendered soluble in bile by aggregation with **water-soluble bile salts and water-insoluble lecithins, both of which act as detergents.** ▪ When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals. (Simply; 1- the cholesterol increase 2- cholesterol will not be soluble 3- cholesterol precipitate and form stones.) **Cholesterol gallstone formation involves four simultaneous defects:** 1- Supersaturation of bile with cholesterol is the result of hepatocellular hypersecretion of cholesterol. 2- Gallbladder hypomotility ensues. It promotes nucleation typically around a calcium salt crystal nidus[1]. 3- Cholesterol nucleation in bile is accelerated. 4- Mucus hypersecretion in the gallbladder traps the crystals, permitting their aggregation into stones. 5- Prolonged fasting, pregnancy, rapid weight loss, total parenteral nutrition, and spinal cord injury also promote stone formation.	▪ Pathogenesis of pigment stones is based on the presence of unconjugated bilirubin in the biliary tract (which is poorly soluble in water) and precipitation of calcium bilirubin salts. ▪ Thus, infection of the biliary tract, as with ***Escherichia coli* or *Ascaris lumbricoides*** or by the liver fluke ***Opisthorchis sinensis,*** increases the likelihood of pigment stone formation. ▪ Chronic hemolytic conditions also promote formation of unconjugated bilirubin in the biliary tree. Black stones are harder
Morphology	Arise exclusively in the gallbladder and are composed of cholesterol ranging from 100% pure (which is rare) down to around 50%. ▪ Pale yellow, round to ovoid to faceted, and have a finely granular, hard external surface. ▪ **Stones composed largely of cholesterol are radiolucent; only 10% to 20% of cholesterol stones are radio-opaque** (because of the small amount of calcium.)	Black and brown. ▪ "Black" pigment stones are found in sterile gallbladder. ▪ "Brown" pigment stones are found in infected intrahepatic or extrahepatic bile ducts. ▪ Both are soft and usually multiple. ▪ Brown stone are greasy. ▪ **Because of calcium carbonates and phosphates, approximately 50% to 75% of black stones are radio-opaque** (High percentage radio-opaque because it contains high amount concentrations).

[1] The point of origin or focus of a disease process.

Cholesterolosis:

An incidental finding, is **cholesterolosis**. 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"

Under microscope:
infiltration of lamina propria by foamy histiocytes.
Grossly:
Velvet green and in between is yellow flecks which will produce strawberry gallbladder appearance.



Clinical Features:

- 70% to 80% of patients remain asymptomatic throughout their lives.
- Symptoms: spasmodic or "colicky" upper quadrant pain, which tends to be excruciating (very painful).
- It usually follows a fatty meal which forces a stone against the gall bladder outlet leading to increased pressure in the gall bladder causing pain. Pain is localized to right upper quadrant or epigastrium that may radiate to the right shoulder or the back
- It is usually due to obstruction of bile ducts by passing stones.

Once the stone get passed the bile ducts to the intestine, the pain will stop.

Complications:

- Obstructive cholestasis.
- Pancreatitis.
- Perforation.
- Fistulas.
- Inflammation of the biliary tree (cholangitis)
- Empyema (pus accumulation).
- 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, or "gravel," that are more dangerous.
- Occasionally a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus" or Bouveret syndrome).
- Gallstones are associated with an increased risk of gallbladder carcinoma.

Large calculi can be dangerous sometimes, by blocking the bile ducts which will result in a swollen gall bladder, and this may lead to an acute on chronic cholecystitis.

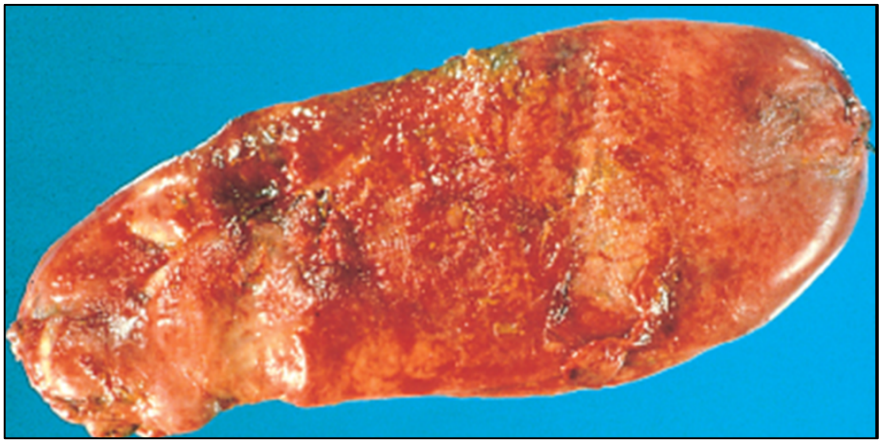
Acute pancreatitis is the most dangerous one.

Cholecystitis:

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

Acute Cholecystitis:

	Acute calculous cholecystitis	Acute acalculous cholecystitis
Definition	An acute inflammation of the gallbladder, precipitated 90% of the time by obstruction of the neck or cystic duct. ○ It is the primary complication of gallstones and the most common reason for emergency cholecystectomy.	Occurs in the absence of gallstones, generally in severely ill patients. Is acute cholecystitis always caused by stones? No.
Clinical Features	Progressive right upper quadrant or epigastric pain, frequently associated with mild fever, anorexia, tachycardia, sweating, and nausea and vomiting. The upper abdomen is tender. Most patients are free of jaundice May appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical intervention. Just like the symptoms in acute pancreatitis.	Tend to be 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. (Because it's masked by other conditions, it is often detected late when the complication has already occurred)
Pathogenesis	Results from chemical irritation and inflammation of the obstructed gallbladder. *These events occur in the absence of bacterial infection*; only later in the course may bacterial contamination develop. Acute calculous is aseptic, just a chemical irritation.	Most cases of occur in the following circumstances: (1)Severe burns. (2)Multisystem organ failure. (3)Sepsis. (4)The postpartum state. (5) The postoperative state after major, nonbiliary surgery. (6) Severe trauma (motor vehicle accidents, war injuries). (7) Prolonged intravenous hyperalimentation.



Morphology: Under the microscope, can someone knows if it's caused by stones or not? No

- In acute cholecystitis, the gallbladder is usually enlarged and tense, and bright red to green-black. The serosal covering is frequently layered by fibrin and, in severe cases, by exudate.
- There are **no** morphologic differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the former.
- In calculous cholecystitis, an obstructing stone is usually present in the neck of the gallbladder or the cystic duct.
- The gallbladder lumen is filled with a cloudy or turbid bile that may contain fibrin and frank pus, as well as hemorrhage. When the contained exudate is virtually **pure pus**, the condition is referred to as **empyema of the gallbladder**.
- **In mild cases,** the gallbladder wall is thickened, edematous, and hyperemic.
- **In more severe cases**, it is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**, with small-to-large perforations.

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. It is associated with cholelithiasis in over 90% of cases.

Clinical Features

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

  A sense of fullness, specially when they eat butter.
- Patients often have **intolerance** to fatty food, belching and postprandial epigastric distress, sometimes include nausea and vomiting.

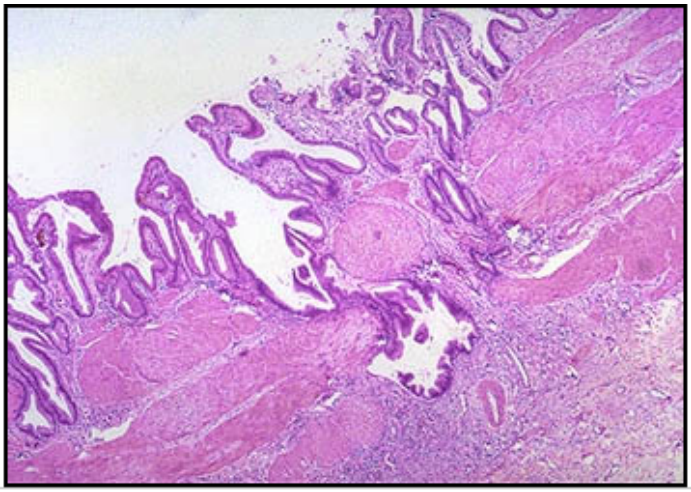
Morphology

- The morphologic changes in chronic cholecystitis are extremely variable and sometimes minimal. Gall bladder may be contracted (fibrosis), normal in size or enlarged (from obstruction). The wall is variably thickened. Stones are frequent.
- On histology, the degree of inflammation is variable. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses**) may be quite prominent.
- Finally, an atrophic, chronically obstructed gallbladder may contain only clear secretions, a condition known as **hydrops of the gallbladder**

Rare conditions

- Rarely, extensive dystrophic calcification within the gallbladder wall may yield a **porcelain gallbladder** (hard gallbladder), notable for a markedly increased incidence of associated cancer.
- **Xanthogranulomatous cholecystitis** is also a rare condition in which the gallbladder is shrunken, nodular, fibrosed and chronically inflamed with abundant lipid filled macrophages.

Under microscope:
Acute cholecystitis: proliferation of fibroblasts.
Chronic cholecystitis: thickening of the muscularis propria



Rokitansky-Aschoff sinuses (outpouchings of the mucosal epithelium through the muscular wall of the gallbladder) may be seen in chronic cholecystis

On histology, we can see lymphocytes. Porcelain bladder on x-rays will appear as bright white.

Xantho- means yellow, and in xanthogranulomatous cholecystitis you can see foamy histiocytes.

Hydrops of the gall bladder is very rare.

If the epithelium penetrates the wall, it means either cancer or diverticulum.

Acute on chronic cholecystitis is a chronic cholecystitis and on it is a proliferation (acute).

Complications of Acute & Chronic Cholecystitis:

1- Bacterial superinfection with cholangitis or sepsis.

2- GB perforation & local abscess formation.

3- GB rupture with diffuse peritonitis.

4- Biliary enteric (cholecystenteric) fistula with drainage of bile into adjacent organs, and potentially gallstone-induced intestinal obstruction (ileus).

5- Aggravation of pre-existing medical illness, with cardiac, pulmonary, renal, or liver decompensation.

Check Your Understanding

MCQs:

1. **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. Which of the following metabolic changes is most likely associated with the formation of gallstones in this patient?**
   A. Increased hepatic cholesterol secretion
   B. Decreased serum albumin
   C. Increased bilirubin uptake by the liver
   D. Increased hepatic calcium secretion

2. **For the patient described in Question 1, 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

3. **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. 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 gallbladder
   D. Adenocarcinoma of the pancreas

4. **Patient presents to the hospital with a long history of intolerance to fatty food, saying they get a sense of fullness specially after they eat butter. Histological findings include Rokitansky-Aschoff sinuses. What is most likely the diagnosis?**
   A. Acute cholecystitis
   B. Chronic cholecystitis
   C. Adenocarcinoma of the gallbladder

1:A 2:D 3:A 4:B
* 1,2,3 from 434.

5. **A patient presented to the ER with progressive upper right abdominal pain, tachycardia, sweating and nausea. His temperature was 37.8 ° C, upon abdominal examination his upper abdomen is tender. After several investigations, it was discovered that he has multiple gallstones. What is most likely the diagnosis?**
   A. Acute calculous cholecystitis
   B. Acute acalculous cholecystitis
   C. Chronic Cholecystitis

6. **A strawberry gallbladder appearance is a feature of?**
   A. Acute calculous cholecystitis
   B. Acute acalculous cholecystitis
   C. Chronic Cholecystitis
   D. Cholesterolosis

7. **Presence of unconjugated bilirubin in the biliary tract indicates which of the following?**
   A. Pigment stones
   B. Cholesterol stones
   C. Chronic Cholecystitis
   D. Cholesterolosis

8. **A woman presented to the hospital with cholesterol stones, which of the following could be the precipitating factor?**
   A. Chronic hemolytic syndromes
   B. Biliary infection
   C. Oral contraceptives
   D. Ileal disease

9. **The incidence of gangrene and perforation of the gallbladder is much higher in?**
   A. Acute calculous cholecystitis
   B. Acute acalculous cholecystitis
   C. Chronic Cholecystitis
   D. Cholesterolosis

10. **Which of the following is not a complication of cholecystitis?**
   A. Bacterial superinfection with cholangitis or sepsis.
   B. Alzheimer
   C. GB perforation & local abscess formation.
   D. GB rupture with diffuse peritonitis

5:A 6:D 7:A 8:C 9:B 10:B

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق