جامعة الملك سعود
King Saud University

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GNT pathology cases file
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Pathology

Gall bladder Disorders

439

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- Important
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" اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا "

Objective

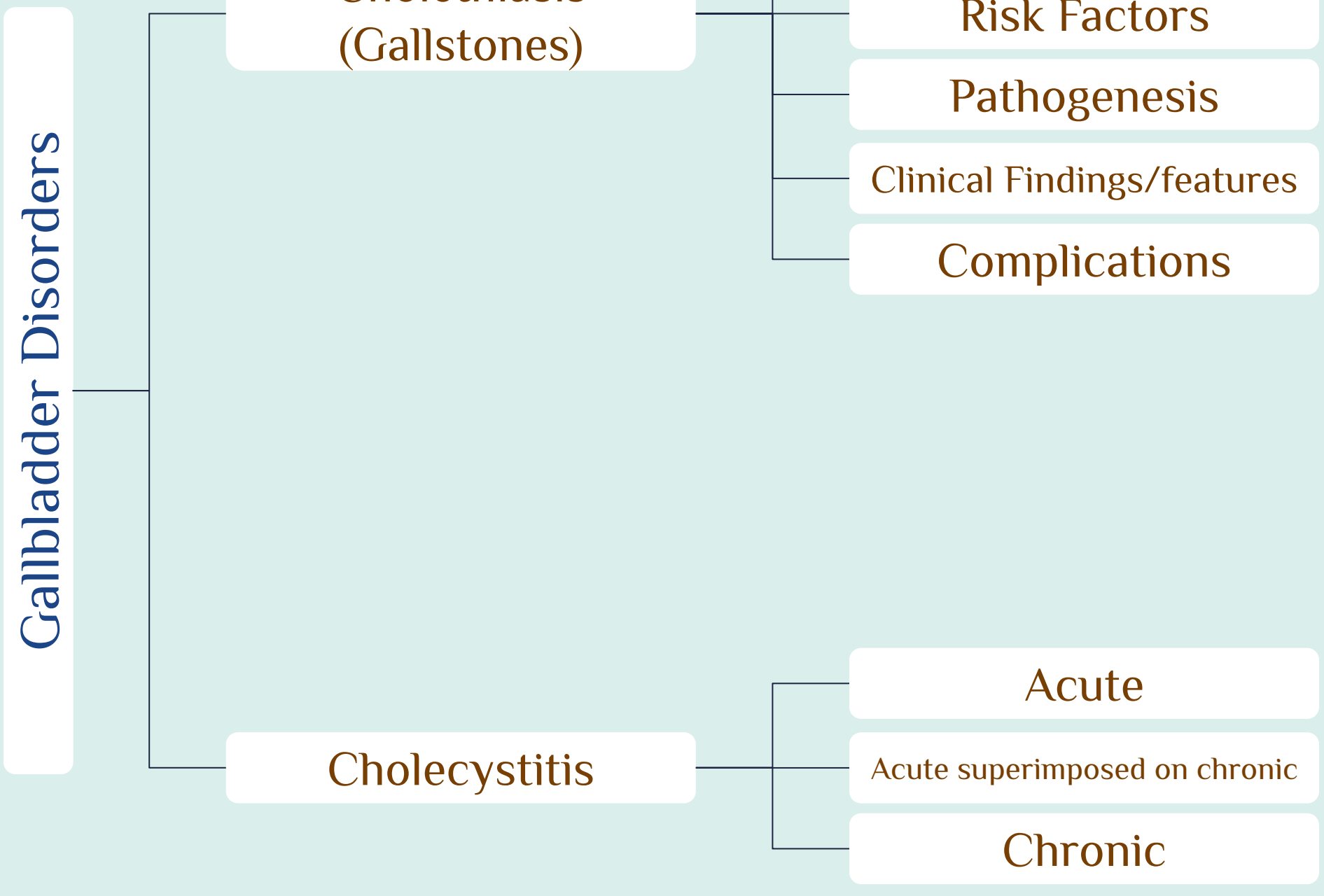
01 Recognize the predisposing factors of cholecystitis.

02 Describe the pathological features different types of cholecystitis.

03 Describe the clinical features different types of cholecystitis.

04 Understand the pathogenesis of acute and chronic cholecystitis

Overview

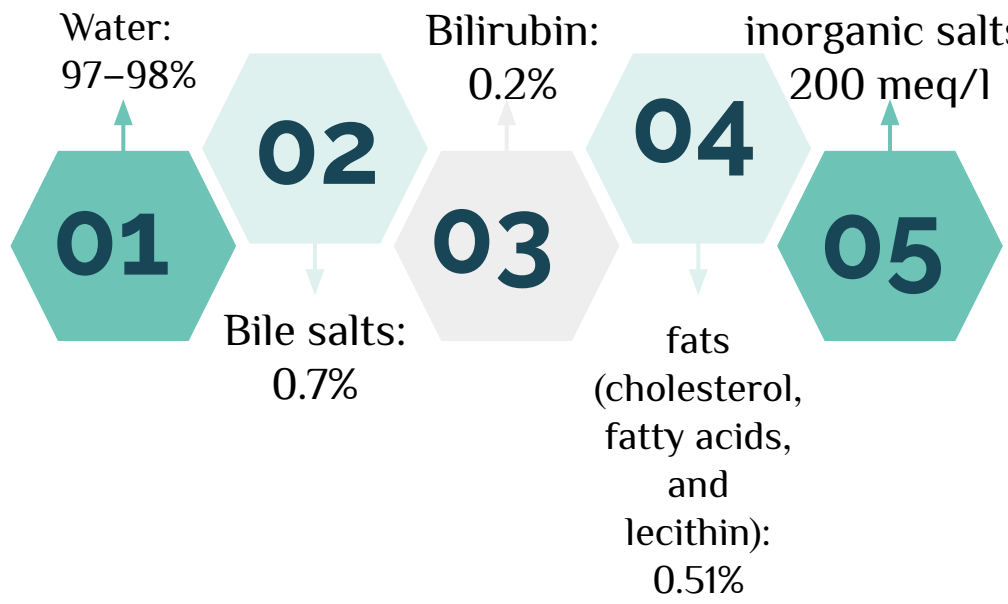


Cholethiasis (Gallstones)

Introduction

Bile content

Male's slide



The two main pigments of bile are:

1. Bilirubin, which is **orange–yellow**
2. Biliverdin , which is **green**

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

Definition

- 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 CBD.

★ There are two main types of gallstones:

1. **Cholesterol Stones:** about 80% are cholesterol stones containing crystalline cholesterol monohydrate
2. **Pigment Stones:** about% are pigment stones Composed predominantly of **bilirubin calcium salts**

Cholethiasis (Gallstones)

Prevalence of gallstones

Female's slide

01 **Age and gender:** The prevalence of gallstones increases throughout life (especially above age of 40). The prevalence in women of all ages is about twice as high as in men

02 **Ethnic and geographic:** Cholesterol gallstone prevalence approaches 50% to 75% in certain Native American populations (Pima, Hopi, and Navajo), seems to be related to biliary cholesterol hypersecretion

03 **Heredity:** A positive family history imparts increased risk, associated with impaired bile salt synthesis and secretion

04 **Environment: 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

05 **Acquired disorders:** Any condition in which **gallbladder motility is reduced** predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury

Risk Factors of cholesterol stones

1. Advancing age
2. Hyperlipidemia
3. Obesity
4. Rapid weight reduction
5. Gallbladder stasis "↓motility"
6. Inborn disorders of bile acid metabolism
7. Female sex hormones
   - Female gender
   - Oral contraceptives
   - Pregnancy
8. Demography
   - Northern Europe, North and South America, Native Americans, Mexican Americans

The 5 F's risk factors:

1) Fat
2) Forty (more than 40 YO)
3) Female
4) Fertile (increased estrogen/pregnancy)
5) Fair (gallstones more common in Caucasians)

Risk Factors of Pigment stones

1. Chronic hemolytic syndromes
   - (e.g., sickle cell, anemia, hereditary spherocytosis
2. Biliary infection
3. Gastrointestinal disorders
   - 1- Ileal disease (e.g., Crohn disease), ileal resection or bypass, 2. cystic fibrosis with pancreatic insufficiency
4. Demography
   - Asian more than Western, rural more than urban

Cholethiasis (Gallstones)

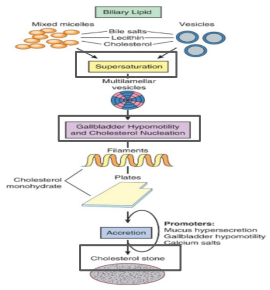
Pathogenesis of Cholesterol Stones

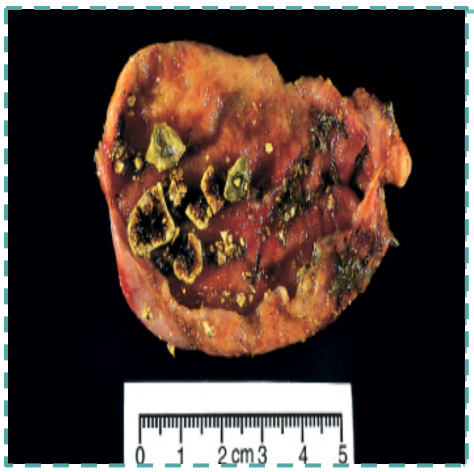
- Cholesterol is rendered soluble in bile by aggregation with water-soluble bile salts and water-insoluble lecithins, both of which act as detergents.
- When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.
- **Cholesterol gallstone formation involves three simultaneous defects** :

1. **Supersaturation** of bile with cholesterol: the result of hepatocellular hypersecretion of cholesterol.
2. **Gallbladder hypomotility** : It promotes nucleation typically around a calcium salt crystal nidus.
3. **Mucus hypersecretion** in the gallbladder: This traps the crystals, permitting their aggregation into stones.

The four contributing factors for cholelithiasis:

1. Supersaturation
2. Gallbladder hypomotility
3. Crystal nucleation
4. Accretion within the gallbladder mucous layer





Morphology of cholesterol stones

- Cholesterol stones arise exclusively in the gallbladder and are composed mainly of cholesterol ranging from 100% pure (which is rare) down to around 50%
- **pale yellow** "the color of cholesterol", 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 radiopaque.

Pathogenesis of Pigment Stones

- Pathogenesis of pigment stones is based on the presence in the biliary tract of **unconjugated bilirubin** (which is poorly soluble in water) and precipitation of **calcium bilirubin salts**.
- 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 "the most common cause"

Morphology of pigment stones

Pigment gallstones are **black and/or brown**:

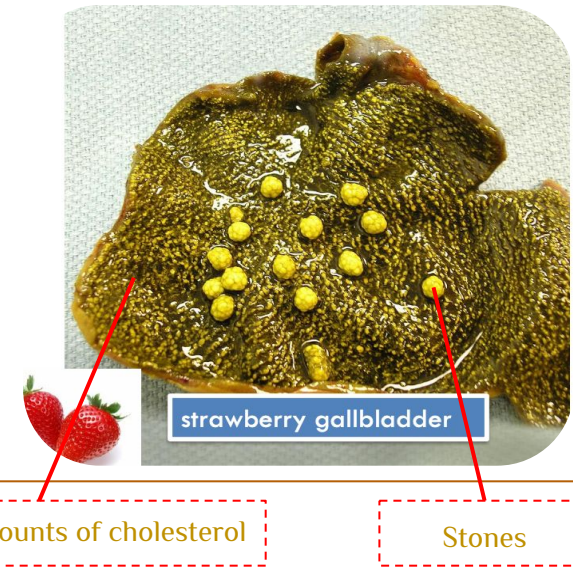
- "Black" pigment stones are found in sterile gallbladder
- "Brown" pigment stones are found in infected intrahepatic or extrahepatic bile ducts

Both are soft and usually multiple , Brown stone are greasy Because of **calcium carbonates** and phosphates, approximately **50% to 75% of black stones are radiopaque**

Cholethiasis (Gallstones)

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**"



Clinical Features of Gallstones

- 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 → severe abdominal pain (especially after a fatty meal) .

Complications of Gallstones

1. Empyema (Pus)
2. Gallstone ileus (Obstructive cholestasis)
   - 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 the more dangerous.
   Occasionally, a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus")
3. Perforation and Fistula (between gallbladder and other organs)
4. Pancreatitis
5. Inflammation of the biliary tree (cholangitis)
6. Gallbladder carcinoma
   - The most important risk factor associated with gallbladder carcinoma is gallstones (cholelithiasis), which are present in 95% of cases

Cholecystitis

- Inflammation of the gallbladder
- It almost always occurs in association with gallstones

- **Acute**
  - Acute **calculous** cholecystitis
  - Acute **a**calculous cholecystitis
    - Postoperative , severe trauma , severe burns , multisystem organ failure , sepsis ,postpartum state
- **Acute superimposed on chronic**
- **Chronic**

1. Acute **calculous** cholecystitis

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

Pathogenesis

Female's slide

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

1. Phospholipases derived from mucosa → hydrolyze biliary lecithin to lysolecithin which is toxic to mucosa
2. Disruption of normally protective glycoprotein mucous layer → exposes mucosal epithelium to detergent action of bile salts
3. Prostaglandins released within distended GB wall → enhance mucosal & mural inflammation
4. Distention & ↑ intraluminal pressure → compromise blood flow to mucosa

Cross Morphology

- Enlarged and tense, and **bright red to green-black**
- Serosa is frequently covered by **fibrin** or fibrinopurulent **exudate** ، **hemorrhage**
- The lumen is filled with a cloudy or pure pus, **"empyema"**
- The wall is thickened, edematous, 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

- Severe, usually constant progressive **right upper quadrant abdominal pain or epigastric pain** , radiating to right shoulder
- May appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical intervention.
- Lasts > 6 hrs, Recurrence is common
- **Mild Fever**, nausea, leukocytosis & prostration are classic, RUQ tenderness & rigidity
- Conjugated hyperbilirubinemia "if CBD "common bile duct" is obstructed"
- Mild attacks usually subside spontaneously within 1-10 days
- ~ 25% are ill enough → emergency surgery

2. 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
- Most occur in seriously ill patients

Occurs in the following Circumstances

Female's slide

1. Following major surgery
2. Severe trauma
3. Severe burns
4. Multisystem organ failure
5. Sepsis
6. The postpartum state
7. Other contributing factors: dehydration, GB stasis & sludging, vascular compromise, and bacterial contamination

3. Chronic cholecystitis

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

Grossly

Variable and sometimes minimal

- Gallbladder is small, normal in size or enlarged (from obstruction)
- Thickened wall contracted "**fibrosis**"
- Almost always contains stones
- the wall is variably thickened , stone are frequent

Microscopic

- Chronic inflammation in the wall with submucosal & subserosal fibrosis
- Prominent **Rockitansky-Aschoff sinuses** "outpouchings of mucosal epithelium through GB wall
- **Xanthogranulomatous cholecystitis** abundant lipid filled macrophages
- Lymphocytic infiltration

Clinical Features

- Symptoms are similar to those of the acute form and range from biliary colic to indolent right upper quadrant pain and epigastric distress.
- Patients often have intolerance to fatty food, belching and postprandial epigastric distress, sometimes include nausea and vomiting.

Complications

- **Bacterial superinfection → cholangitis or sepsis**
- Gallbladder perforation → local abscess
- Gallbladder rupture → diffuse peritonitis
- Biliary enteric fistula → entry of air and bacteria into biliary tree & possible gallstone-induced intestinal obstruction "ileus"
- Aggravation of pre-existing medical illness → cardiac, pulmonary, renal, or liver decompensation

Carcinoma of the Gallbladder

This whole page was found in the girls slides

Introduction

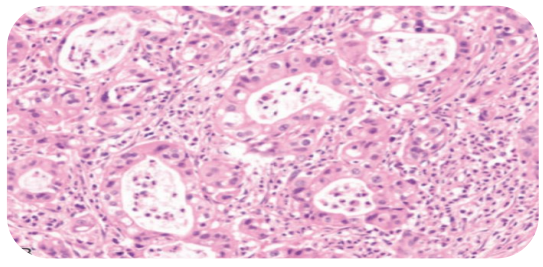
- Most common malignant tumor of the extrahepatic biliary tract
- Mainly in 7th decade of life
- Slightly more common in women
- Usually discovered late “unresectable”; mean 5 - year survival rate is 5-12%

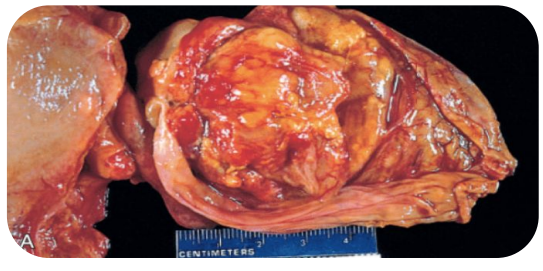
Risk Factors

1. Gallstones (found in 95% of cases)
2. Infections of the biliary tree
3. Both ➔ chronic inflammation
4. Primary sclerosing cholangitis

Morphology

Gross patterns of growth	Microscopic
❖ **1. Exophytic:** Irregular, cauliflower-like mass growing into lumen & invading the underlying wall at same time ❖ **2. Infiltrating:** More common pattern of growth üPoorly defined area of diffuse wall thickening & induration	❖ Most are adenocarcinomas ❖ 5% SCC 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

Summary

This summary was taken from Robbins

- Gallbladder diseases include cholelithiasis and acute and chronic cholecystitis, and gallbladder cancer.
- Gallstone formation is a common condition in Western countries. The great majority of the gallstones are cholesterol stones. Pigmented stones containing bilirubin and calcium are most common in Asian countries, due to the higher incidence of chronic hemolytic disorders and liver fluke infestations in these locales.
- Risk factors for the development of cholesterol stones are advancing age, female gender, estrogen use, obesity, and heredity.
- Cholecystitis almost always occurs in association with chole- lithiasis, although in about 10% of cases it occurs in the absence of gallstones.
- Acute calculous cholecystitis is the most common reason for emergency cholecystectomy.
- Gallbladder cancer is almost always associated with gallstones. Because of the advanced stage at diagnosis, it has a very poor prognosis.

Good luck !

See you next Block...

QUIZ!

MCQs

01 | which one of the following is a risk factor for Cholesterol stones?			
A) Biliary infections	B) Gastrointestinal disorders	C) Hyperlipidemia	D) Chronic hemolytic syndromes
02 | 56 years old female was brought to the ER by her son due to right upper quadrant pain for several hours, her son reports that his mom is on statins but she doesn't take her medications regularly, her BMI is 35 and she appears pale and tired what is the most likely diagnosis?			
A) Pancreatitis	B) liver cancer	C) gallstones	D) cirrhosis
03 | 43 years old female was diagnosed with hemolytic anemia, she presents to the ER with abdominal pain that is colicky in nature, radiological investigation reveals radiopaque stones what is the most likely contributing factor to her condition?			
A) excess bilirubin	B) hypercholesterolemia	C) oral contraceptives	D) biliary tract infections
06 | 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 1.0mg/dL, AST of 25U/L, ALT of 35U/L, alka- line phosphatase of 220U/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 follow- ing is the most likely diagnosis?			
A) Adenocarcinoma of the gallbladder	B) Acute pancreatitis	C) Acute cholecystitis	D) Primary biliary cirrhosis

MCQs Answer key	01	02	03	04	05	06
	C	C	A	A	D	A

" اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين "

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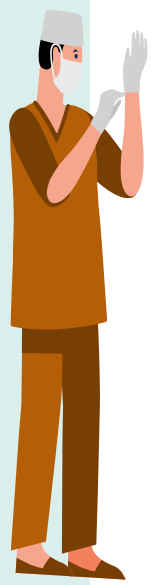

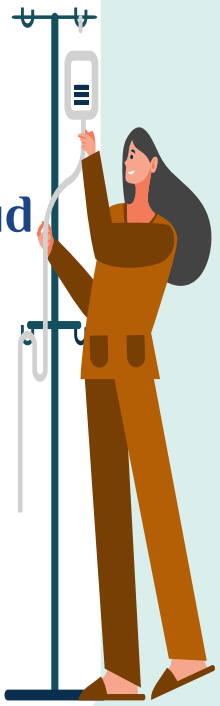

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