# GIS 15

## PATHOLOGY


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Here's a short list of the things we'll be going over to make this sheet seem a little less boring/intimidating... ☺



**Anything written in a box** is extra info from the book for clarification.
**All the images** are taken from the book, and **ARE NOT in the slides.**
**Anything written in the slides that** hasn't been mentioned by the professor will be underlined, written in square brackets and in [red].

# BILIARY ATRESIA

↳ *The complete or partial obstruction of the lumen of the extrahepatic biliary tree.*

➢ ***When does it occur?*** Within the first 3 months of life

↳ Occurs in about 1:10,000 live births

➢ ***It is a cause of:***

1. Neonatal Cholestasis [**1/3 of cases]**
2. Death from liver disease in early childhood **(MOST COMMON CAUSE).**

**Side note (from the book):** Approximately 50% to 60% of children referred for liver transplantation have biliary atresia.

➢ ***Characterized*** *by:*
**Rapid progression to cirrhosis** within 3 to 6 months.

➢ ***Pathogenesis*:**
**There are two types of biliary atresia:**

1. **Fetal form**

- 20% of the cases
- Associated with:

- Other developmental malformations, anomalies and malrotation of the abdominal viscera
- [Interrupted inferior vena cava]
- [Polysplenia]
- [Congenital Heart Disease]
- [Aberrant intrauterine development of extrahepatic biliary tree.]

## 2. ***Perinatal Form (more common)***

- Characterized by **normal development of the biliary tree.**
- However, the normal biliary tree is injured/destroyed following birth, presumably due to:
  - Viral infection:
    - Reovirus
    - Rotavirus
  - Genetic abnormalities

I say **presumably**, since the etiology of perinatal biliary atresia is unknown. However, the causes I have just mentioned are the prime suspects.

## ➢ ***Morphology (histology) of Biliary Atresia:***

1. **Inflammation (edema)**
2. **Fibrosing narrowing (stricture) of the hepatic or common bile ducts**
3. Bile duct proliferation **(proximally)**
4. [Periductular inflammation of the intrahepatic biliary tree]
5. [Portal tract edema and fibrosis]
6. Cholestasis (Prominent)

## ➢ ***Clinical Features in Infants:***

1. Associated with neonatal cholestasis.
2. Infants have normal **birth weight.**
3. **Postnatal weight gain**
4. [Females > Males]
5. Have hyperbilirubinemia
6. Stool becomes acholic (Pale in color): Due to absence of the biliary system.

## CHOLESTASIS

↳ *Stone formation within the biliary system.*

↳ *It is a common condition.*

Caused by extrahepatic or intrahepatic obstruction of bile channels or by defects in hepatocyte bile secretion.

- **10-20%** of adults in ***developed*** countries have gallbladder stones.
- **20-40%** incidence in Latin America. (higher)
- **3-4%** incidence in Asia. (low)

## ➢ ***TYPES OF STONES***

1. **Cholesterol stones** (80% of stones in western countries):
   Made up of **crystalline cholesterol monohydrate.**
2. **Pigment stones** (20%): **Made of bilirubin calcium salts.**

## ➢ ***Risk Factors*** The table on the right is from the book

## Cholesterol Stones:

1. Geographical area
   ↳ (more common in developed countries)
2. Age (Old age → Higher risk)
   - **Older than 80** → 25-30%
   - **Younger than 40** → 5-6%
3. Sex hormones
   ↳ **Female sex hormones**
4. Gender
   ↳ **Females > Males**
5. Oral contraceptives
   ↳ **More likely in females**
6. Pregnancy
7. Obesity → **Increases risk**
8. Rapid weight reduction
9. Stasis and hypomotility of the gallbladder
   ↳ (Seen during pregnancy and spinal cord injury.)

**Table 16.6 Risk Factors for Gallstones**

| Cholesterol Stones |
|---|
| Demography: Northern Europeans, North and South Americans, 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 |
| Dyslipidemia syndromes |
| **Pigment Stones** |
| Demography: Asian more than Western, rural more than urban |
| Chronic hemolysis (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 |

**RARE RISK FACTORS:**

10. Inborn (inherited) disorders of bile acid metabolism
11. Hyperlipidemia syndrome

***80%*** *of the cases have no identifying risk factor other than* ***age*** *&****gender.***

## Pigment Stones

1. Geographical area: More common in Asian countries than in western countries

2. Presence of chronic hemolytic anemia: Characterized by an increase in unconjugated hyperbilirubinemia.
3. Biliary infections
4. GI disorders

## ➢ ***Pathogenesis***

## Cholesterol Stones:

- Normally: Cholesterol is eliminated from the body through bile. How?

↳ Cholesterol stones are **water insoluble** (cholesterol is insoluble).

↳ Cholesterol becomes water soluble through **aggregation with bile salts & lecithin** to enhance their excretion.

- This is associated with the supersaturation of bile by cholesterol → Forms aggregates of cholesterol monohydrate → **Cholesterol stones** formed

- **Prerequisites for cholesterol stone formation:**

1. Supersaturation of bile with cholesterol.
2. Nucleation or precipitation of organic and inorganic Ca++ salts → forming a nidus.
3. Decreased mobility of the gallbladder → Gallbladder stasis
4. Mucus hypersecretion → Helps trap the crystals (monohydrate crystals).

## Pigment Stones:

- Are composed of insoluble Ca++ salts and inorganic Ca++ salts of unconjugated bilirubin.

- These salts (the aggregation) are enhanced by infection:
  - **Bacteria**: E coli
  - **Parasites**: Ascaris

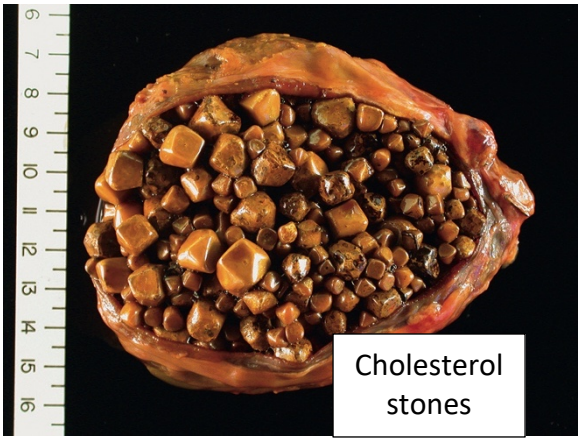
  ↳ Enhances the release of microbial β-glucuronidase, which hydrolyzes bilirubin glucuronidase → Unconjugated bilirubin

- [Hemolytic anemia]

## ➢ ***MORPHOLOGY***

## Cholesterol Stones:

- Form exclusively in the gallbladder.
- Consists of **50-100% cholesterol**
- **Ovoid** and **firm**
- Usually **multiple** but can be a single stone.



Cholesterol stones

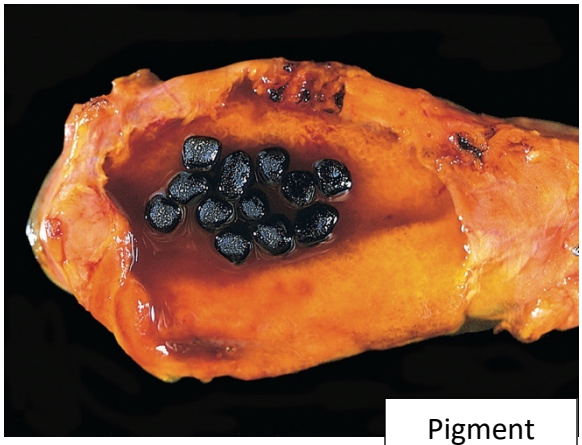
- **Faceted surfaces**
  - ↳ Due to pressure induced by the presence of **multiple stones (pushing against the wall).**
- If *pure*: They are **radiolucent**
- If *calcium salt precipitate* is found within the stones:
  They become **radiopaque.**
- **20%** of cholesterol stones are **radiopaque** (contain calcium carbonate).

## Pigment Stones

- Occur anywhere within the biliary tree.

**Black** or **Brown** (depending on **purity**)

- **50-70%** are **radiopaque** (due to the presence of *calcium salts*).



Pigment stones

➢ ***CLINICAL FEATURES*** (more or less similar in both types of stones)

- 70-80% of them are **ASYMPTOMATIC.**
- 1-3% of the patients become **SYMPTOMATIC** per year.

1) Constant/Colicky pain (main presentation). This occurs due to inflammation, or due to biliary tree obstruction.

The pain usually presents in the right upper quadrant or epigastric regions.

2) Empyema (*severe complication)*
   - ↳ **Accumulation of purulent bile in the gallbladder.**
3) Perforation of the wall of the gallbladder *(severe complication)*
4) Fistula formation (*severe complication)*
   - ↳ **Connecting to the other bowel**
5) Obstructive cholestasis (*severe complication)*
   - ↳ If the **constriction occurs in the major bile duct** → Jaundice
6) Pancreatitis (*severe complication)*
   - ↳ If the **pancreatic duct** is obstructed by the stones
7) Intestinal obstruction (*gallstone ileus)*

# CHOLECYSTITIS

↳ *Common clinical condition*
↳ Either **acute**, **chronic,** or **acute on top of chronic** inflammation
↳ **Almost always associated with the presence of stones.**

## ➢ ***CLINICAL FEATURES***:

### A. Acute Calculous Cholecystitis

Acute inflammation of the gallbladder that contains stones, and is the most common major complication of gallstones.

- **Steady upper abdominal pain** radiating to the right shoulder. Colicky pain when stones are present in the neck of the gallbladder.)
- **Fever, nausea, and leukocytosis.**
- **Obstruction of the common bile duct** due to the presence of stones which causes *severe pain.*
- **Tenderness in the right subcostal region and shoulder.**
- **Mild attacks of acute cholecystitis**→ Subside spontaneously in **(1-10 days).**
  - ↳ Recurrence in these patients is common.
- [25% require surgical intervention.]

### **B.** Acute Acalculous Cholecystitis

[5-12% of gallbladders removed for acute cholecystitis contain NO gallstones.]

They have symptoms that are obscured by the generally severe clinical condition that involves other organs.

## ➢ ***PREDISPOSING FACTORS:***

1. **Post-operative status after major non-biliary surgery.**
   - ↳ The **MOST COMMON** predisposing factor.
2. **Severe trauma (e.g. motor vehicle crashes)**
3. **Severe burns**
4. **Sepsis**

## ➢ ***MECHANISM***

- **Dehydration**
- **Gallbladder stasis**
- **Vascular compromise**
- **Bacterial contamination**

This obstruction to bile flow is due to the presence of stones leads to chemical injury of the soft tissue.

## ➢ ***MORPHOLOGY***

- ↳ *Acute cholecystitis is an inflammatory process.*
- ↳ Patients have a different degree/extent of inflammation.

- *GALLBLADDER* ***becomes***
  - ***Enlarged***
  - Tense
- *DISCOLORATION:*
  - [Bright red – Green-black(more severe) or blotchy color]
- *SUBSEROSAL:*
  - **Hemorrhage**
- *SEROSA:*
  - **Covered with fibrin** & **suppurative exudate**.
- *STONES* seen in **90% of cases** in the:
  - Neck of the gallbladder
  - Cystic duct.
- *Gallbladder lumen:*
  - **[Bile becomes** cloudy and turbid**, and may contain fibrin, blood and pus.]**
- *EMPYEMA*

↳ Complication of gallbladder stones: When the gallbladder becomes filled with pus.

GALBLADDER *WALL* becomes

1. Thick
2. Edematous
3. Hyperemic

- *Gangrenous GB* → Necrosis of the gallbladder wall

↳ Due to pressure applied or induced by the stones.

| In Gangrenous Cholecystitis, the gallbladder wall is green-black and necrotic. |
|---|

### ➢ ***Histological Appearance***

The gallbladder wall shows features of acute inflammation: edema, [leukocyte infiltration, and vascular congestion.]

| Along with abscess formation and gangrenous necrosis. |
|---|

## **C.** Chronic Cholecystitis

### ➢ ***Characterized by:***

Recurrent attacks of steady or colicky epigastric or RUQ (Right upper quadrant) pain.

| Chronic cholecystitis may be the sequel to repeated bouts of acute cholecystitis, but in most instances it develops without any antecedent history of acute attacks. |
|---|

## ➢ ***Clinical Features***

- Nausea & vomiting
- Fat intolerance
- Almost always associated with gallbladder stones. (like acute cholecystitis)
- **Obstruction is not a feature. (unlike acute cholecystitis)**

## ➢ ***Mechanism:***

- Occurs due to supersaturation of bile → Leads to inflammation or stone formation.
- Superimposed Infection with:
  - E. coli & enterococci (**In 1/3 of cases)** [can be cultured from the bile.] These patients don't have obvious obstructions as seen in acute cholecystitis

## ➢ ***Morphology of Chronic Cholecystitis***

- Changes are variable & might be minimal.
- Presence of stones is sufficient for Dx.
- Gall bladder may be normal in size, contracted, or enlarged.
- Mucosal ulceration is infrequent due to stones.
- Submucosal & subserosal fibrosis of the GB wall.
- Lymphocytic infiltration of gallbladder wall.

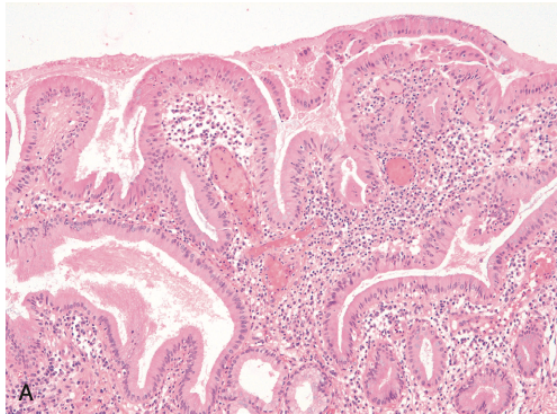



Fig. 16.41 Chronic cholecystitis. (A) The gallbladder mucosa is infiltrated by chronic inflammatory cells.

## ➢ ***Complications of cholecystitis:***

- Cholangitis (due to bacterial superinfection with cholangitis and sepsis)

↳ Infection of the bile ducts mainly due to obstruction-**commonly by stones**

- Perforation forms with local abscess formation.
- Gallbladder can rupture with diffused peritonitis.
- Causes biliary enteric fistula → leads to:
  - Drainage of bile into adjacent organs.
  - Allowance of air and bacteria in to reach the biliary tree.
- If the condition is due to a pre-existing medical condition → aggregation of the general condition of the patient → cardiac/pulmonary or liver decompensation.

➢ ***Other Causes (other than stones) [weren't mentioned by the doctor]***

1. [[Stent or catheters
2. Tumors
3. Acute pancreatitis
4. Benign stricture
5. Fungi, viruses, parasites (infections)]]

[Bacteria enter the biliary tract through the sphincter of Oddi.]

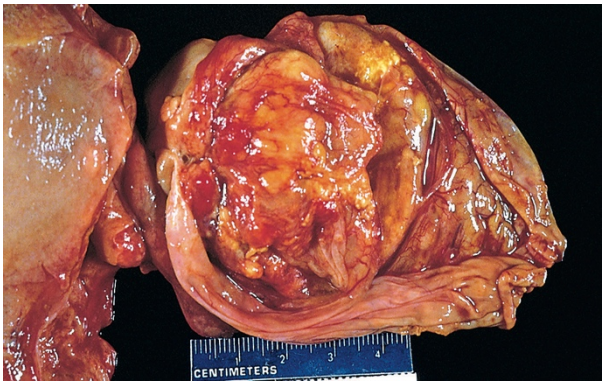
## CARCINOMA OF THE GALLBLADDER

↳ *Tumor that occurs mainly in women (7th decade).*

↳ Carcinoma of the gallbladder is the most common malignancy of the extrahepatic biliary tract.

- **BAD PROGNOSIS:** 5-year survival is about 1%
- Patients have gallstones in **60-90% of cases.**

➢ ***Morphology:***




- Gallbladder tumors can be infiltrating or exophytic.
- Infiltrating tumors in the GB wall are commonly scirrhous (hard to the touch).
- **Most common sites:** Fundus & neck (lateral walls)
- **95% of cases**: They are **MAINLY Adenocarcinomas**
- **5% of the cases: Adeno-squamous, squamous carcinoma** may occur
- **RARELY**: Carcinoid
- **RARELY**: Mesenchymal
- **Local extension** to:
    1. Liver
    2. Cystic duct
    3. Lymph nodes
- **Distant spread** or metastasis to:
    1. Peritoneum
    2. GI
    3. Lungs

➢ ***Carcinoma Clinical Features***

- **Rarely diagnosed pre-operatively** (<20%).

**Presentation**:

1. Nausea
2. Vomiting
3. Pain
4. Jaundice
5. Weight loss
6. Anorexia
7. Symptoms of obstruction and features of acute cholecystitis.
   Which are totally **non-specific** symptoms

## CHOLANGIOCARCINOMA

- *Adenocarcinoma that occurs in the biliary tract within and outside the GB.*
- *Arises from bile ducts within & outside the liver.*
- *Incidence 0.6/100000 in the USA*
- *Males and females are affected the same.*

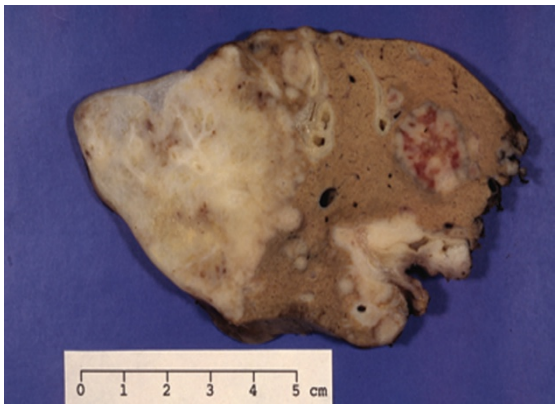



**Fig. 16.38** Cholangiocarcinoma. (A) Multifocal cholangiocarcinoma in a liver from a patient with infestation by the liver fluke *Clonorchis sinensis* (flukes

### ➢ ***Predisposing factors:***

1. Sclerosing cholangitis
2. Congenital fibropolycystic disease of the biliary system.
3. Exposure to Thorostat chemicals
4. Chronic infection by liver flukes.

### ➢ ***Morphology***

- **Adenocarcinoma** with marked **desmoplasia** (growth of fibrous or connective tissue).

### ➢ ***Metastasis***

- **Hematogenous:**
  1. Lung
  2. Bones (vertebra)
  3. Adrenals
  4. Brain (50% of cases)
  5. Regional LN's
- **Lymphatic**: regional LN's (50%)

## ➢ ***Clinical Presentation:***

***Intrahepatic:***

- Detected late
- Appears due to:
    1. Obstruction of bile flow or
    2. Presence of a liver mass.

## ➢ ***Prognosis:***

- **Bad prognosis** (late Dx and detection)

- **1-2 year Survival rate** 13-25%

- Median survival is 6 months

# CARCINOMA OF THE EXTRAHEPATIC BILIARY TREE

↳ *Uncommon*
↳ *Insidious*

- Characterized by: **PAINLESS JAUNDICE**
- ***Males*** > Females between 50-70 years
- **Gallstones in 1/3 of the cases (UNCOMMON WITH EXTRAHEPATIC BILIARY TREE CARCINOMA)**

## ➢ ***Risk increases with:***

1. Biliary tree flukes (Clonorchis)
2. Primary sclerosing cholangitis
3. Inflammatory bowel disease
4. Choledochal cyst
5. Thorostat

# AMPULLARY TUMORS

## ➢ ***Morphology***

- Arise from the ampullary region.
- They are small tumors at the time of diagnosis.
- **Adenocarcinoma** (so far all of them are mainly if not completely adenocarcinomas)
- Increased **mucin** secretion.
- Might show **squamous differentiation.**

# KLASTSKIN TUMOR (SPECIFIC TYPE OF AMPULARRY TUMOR)

↳ *Tumors that arise from the right and left hepatic duct at the liver hilus.*

## ➢ ***Presentation***

- Jaundice
- Discoloration of stool
- Nausea
- Vomiting
- Weight loss
- [In the liver in 50% of the cases]
- Hepatomegaly.
- Enlargement of the gallbladder in [25% of the cases]
- Serum alkaline phosphatase and transaminases levels are abnormally high (indication of malfunction of the liver).
- Increased prothrombin time
- Dark urine

## ➢ ***PROGNOSIS***

- Very bad prognosis →Mean survival: **6-18 months.**