Clinical presentation of liver disease

- Jaundice (mention all causes of direct and indirect hyperbilirubinemia)
- Hepatomegaly (mention causes)
- Symptoms of liver cell failure (enumerate)
- Symptoms of portal hypertension (Enumerate)
- Other clinical presentations: Hepatic encephalopathy - Bleeding tendency
  Pruritus - Palmar erythema - Spider angiomas – Xanthomas - Bone disease
  Hepatopulmonary syndrome - hepatorenal syndrome anorexia - growth failure

Hepatomegaly

Storage:
- Fat: malnutrition, obesity, cystic fibrosis, metabolic liver disease
- Specific lipid storage diseases: Niemann-Pick & Gaucher disease
- Glycogen: glycogen storage diseases, infant of diabetic mother
- others: Alpha-1-antitrypsin deficiency, Wilson disease, Schistosomiasis

Inflammation:
- Acute and chronic viral hepatitis
- Liver abscess
- Autoimmune hepatitis

Infiltration:
- Cystic: choledochal cyst
- Malignant: hepatoblastoma, hepatocellular carcinoma
- Metastases: neuroblastoma, histiocytosis, leukemia, lymphoma

Increased size of the vascular space:
- Budd-Chiari syndrome
- Hepatic veno-occlusive disease
- Right-sided heart failure
- Constrictive pericarditis
- Restrictive cardiomyopathy

Increased size of biliary space:
- Biliary obstruction: biliary atresia
- Congenital hepatic fibrosis
Investigations of Liver Diseases

Laboratory:

1. **Liver Function Tests:**
   - Serum albumin, Prothrombin time
   - Serum bilirubin (Total & Direct)
   - Serum ammonia
   - ALT, AST
   - Alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGT)

2. **Hepatitis markers:** See later

3. **Test for Metabolic diseases:**
   - Enzyme assay as in Gaucher disease, Niemann-Pick disease, glycogen storage disease
   - Gal-1-ph assay in galactosemia
   - Ceruloplasmin level in Wilson disease
   - Alpha 1 antitrypsin in alpha 1 antitrypsin deficiency

Imaging:

1. **Abdominal Ultrasonography** for diagnosis of:
   - Hepatomegaly, hepatic echogenicity, focal lesions
   - Splenomegaly & ascites

2. **Doppler, MRA & MRV** for assessment of:
   - Portal & splenic veins
   - Hepatic artery & hepatic veins

Invasive:

1. **Upper GIT endoscopy** → Esophageal varices
2. **Liver biopsy**: Very helpful in the diagnosis

**N.B.: Wilson disease**

- AR disease Defect: synthesis of (ceruloplasmin) protein (cu transporter) + defective copper excretion in bile
- C.p. : see the figure
- Inv.: ↓ Serum ceruloplasmin "① test"
  ↑↑ Urinary Copper (Before & after D-penicillamine)
- Ttt: Copper chelation with D-penicillamine
**Acute liver failure**

**Definition:** Massive hepatic necrosis $\rightarrow$ acute impairment of liver function.

**Causes:**

1. Autoimmune hepatitis
2. Poisons/drugs: Paracetamol - isoniazid - halothane - mushroom
3. Inborn error of metabolism: Wilson's disease, tyrosinaemia
4. Infection: Viral hepatitis A or B
5. Reye's syndrome

<table>
<thead>
<tr>
<th>LIVER FUNCTION</th>
<th>ACUTE L.C.F.</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of coagulation factors</td>
<td>Bleeding tendency</td>
<td>Plasma transfusion</td>
</tr>
<tr>
<td>Plasma proteins (albumin)</td>
<td>Edema, ascites and electrolyte imbalance</td>
<td>Vit K – H$_2$ Blocker</td>
</tr>
<tr>
<td>Active vit D</td>
<td></td>
<td>Fluid balance</td>
</tr>
<tr>
<td>IGF1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism &amp; Storage of carbohydrate and fat</td>
<td>hypoglycemia</td>
<td>IV glucose 10%</td>
</tr>
<tr>
<td>Blood filtered out of</td>
<td>Hepatic encephalopathy</td>
<td>Gastric wash – enema</td>
</tr>
<tr>
<td>Ammonia &amp; neurotoxins</td>
<td>Infection and fever</td>
<td>Oral neomycin</td>
</tr>
<tr>
<td>Drugs and hormones</td>
<td></td>
<td>Broad spectrum antibiotics</td>
</tr>
<tr>
<td>Infectious bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remove</td>
<td>jaundice</td>
<td>*</td>
</tr>
<tr>
<td>Cholesterol - Bilirubin</td>
<td>pruritis</td>
<td>cholystyramine</td>
</tr>
<tr>
<td>Bile salt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical picture:** see the figure

**Investigations**

- **Laboratory evidence of acute hepatitis**
  - Direct or mixed hyperbilirubinemia
  - **Raised serum transferases** (Levels between hundreds and thousands are common)
    - Raised AST
    - Raised ALT
  - **Evidence of acute hepatic failure (in fulminant hepatitis)**
    - INR $\geq$ 2, uncorrectable with vitamin K
    - or INR between 1.5 and 1.9, uncorrectable with vitamin K plus encephalopathy
    - Rising bilirubin level
    - Low serum albumin level occurs later because of long half-life of albumin
    - Hypoglycemia
    - High blood ammonia
    - Electrolyte disturbance
    - Acid-base balance disturbance

- **Investigation for the cause**

**Treatment:** see the figure
Viral hepatitis by hepatotropic virus

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of virus</strong></td>
<td>Enterovius</td>
<td>Hepadnavirus</td>
<td>Flavivirus</td>
<td>Incomplete</td>
<td>Calcivirus</td>
</tr>
<tr>
<td><strong>Transmission routes</strong></td>
<td>Feco-oral</td>
<td>Parenteral, sexual, vertical</td>
<td>Parenteral, sexual, vertical</td>
<td>Parenteral, sexual, vertical</td>
<td>Feco-oral</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>2-6 weeks</td>
<td>2-6 months</td>
<td>1-5 months</td>
<td>3-6 weeks</td>
<td>2-9 weeks</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td>Anti-HAV IgM</td>
<td>HBsAg, anti-HBc IgM</td>
<td>Anti-HCV HCV-RNA by PCR</td>
<td>Anti-HDV</td>
<td>Anti-HEV</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (HBV)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Chronicity</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Fulminant</strong></td>
<td>Rare</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Clinical picture of acute hepatitis (4 forms):**

a. **Icteric hepatitis:** (Presentation)
   I) **Pre-icteric phase (2 weeks)**
      - Fever, Anorexia, nausea, vomiting, diarrhea & abdominal pain.
   II) **Icteric phase (4 weeks)**
      - Improved previous symptoms with appearance of:
        - Jaundice- Tender hepatomegaly - Dark urine
   III) **Convalescent phase:**
      - Complete resolution (especially in HAV & HEV)
      - Other types (HBV.HCV, HDV) may pass into chronic hepatitis.

b. **Cholestatic hepatitis:**
   - Obstruction to bile flow, jaundice, and pruritis and pale stool are common.

c. **Anicteric hepatitis:**
   - Common in infants featured like gastroenteritis.

d. **Fulminant hepatitis:**
   - Very serious causing acute liver failure (discuss)
   - Bilirubin may not elevate early

**Investigations for a case of hepatitis:**

- **Evidence of acute hepatitis (see before)**

- **Hepatitis markers**
  a. **Hepatitis A:**
     - Anti-HAV antibodies (IgM class) → recent infection
     - Anti HAV IgG antibodies alone → recovery & immunity
  b. **Hepatitis B:**
     - Acute hepatitis B = HBs Ag, followed by anti-HBc IgM
     - Recovery & immunity = anti-HBs antibodies.
     - Chronic infections = HBs Ag persists & anti-HBc Ig G develops.
Hepatitis C:
- Anti-HCV antibody = exposure to infection (does not denote recovery)
- HCV RNA by PCR technique denotes viremia.
- Viral load can be assessed by quantitative PCR for treatment purposes.

Prevention of viral hepatitis

1. General preventive measures
   - **Hepatitis A:**
     - Isolation of acute cases from day care, school during the infectious period (7 days after onset of jaundice).
     - Strict hand washing, particularly after changing diapers and before preparing or serving food is also important.
   - **Hepatitis B:**
     - Prevention of parenteral transmission by
       1. strict screening of blood and blood products,
       2. strict regulations and instrument sterilization for all procedures
   - **Hepatitis C:** Same precautions as hepatitis B.

2. Vaccination
   - **Hepatitis A:** A potent inactivated hepatitis A vaccine is available.
   - **Hepatitis B:**
     - Routine vaccination of all newborns
     - Hepatitis B vaccine was included in program of vaccinations in Egypt since 1993.
     - Vaccination should also target high risk groups:
       e.g. thalassemics and hemophilics receiving repeated blood and blood products.
     - Patients with chronic liver disease must also be protected from superadded hepatitis A or B infections.
   - **Hepatitis C:** No available vaccine
   - **Hepatitis D:** Vaccination against hepatitis B.

**Chronic hepatitis**

**Definition:** Continuing inflammatory liver disease > than 6 months.

**Causes:**
1. Autoimmune hepatitis
2. Chronic infection: HBV, HDV, and HCV
3. Chronic inflammatory bowel disease (ulcerative colitis – sclerosing cholangitis)
4. Drug-induced: Rifampicin, isoniazid, nitrofurantoin
5. Errors of metabolism as Wilson disease – alpha 1 antitrypsin - cystic fibrosis.
6. Non alcoholic fatty liver disease
   - **Incidence:** Most common cause in developed countries
   - **Presentation:** Obese children – lethargy right upper quadrant pain
Clinical picture

A. Acute hepatitis which fails to resolve within 6 months
B. Insidiously diagnosed in an asymptomatic child or present with
   - Firm hepatomegaly
   - Hepatosplenomegaly
   - Symptoms of chronic liver cell failure: Jaundice – bleeding – Ascites – spiders – palmer erythema

C. Other symptoms of the cause
   - Neurological changes in Wilson
   - Skin rash, arthritis and hemolytic anemia in autoimmune hepatitis
   - GIT manifestation in ulcerative colitis

Investigation

- Liver function test: abnormal
- Abdominal ultrasound: assess liver size and texture – spleen – Ascites
- Liver biopsy to assess
  - Degree of inflammation
  - Stage of fibrosis
- Test for the cause
  - Hepatitis markers for hepatitis B,C
  - Positive autoantibodies, e.g. antinuclear antibodies (ANAs) or liver/kidney microsomal antibodies (LKMs) in autoimmune hepatitis
  - Ceruloplasmin and urinary copper in Wilson disease

Complications:

Treatment:

According to the cause
- Prednisolone and azathioprine in autoimmune
- Antiviral (ribavirin – interferon) in viral hepatitis
- Wilson → copper chelating agents

Liver transplantation:
- Indication: end stage LD
- Prognosis: 80% survival with good quality of life
- Mechanism in children in Egypt: living related donor
- Started in Egypt in 2001
Neonatal Cholestasis

**Definition:** Failure of normal amount of bile to reach duodenum due to liver or biliary

**Causes of cholestasis:**
1. **Idiopathic neonatal hepatitis** (giant cell hepatitis):
   - The cause - associated with IUGR
2. **Infections**:
   - Bacterial: neonatal sepsis, urinary tract infection
   - Viral: CMV - Rubella
   - Protozoal: toxoplasma
3. **Metabolic**:
   - Galactosemia
   - Tyrosinemia
   - **Alpha-1- antitrypsin deficiency**: AR – associated with emphysema later on
   - **Inborn error in bile acid biosynthesis**:
4. **Familial cholestatic syndromes**:
   - Paucity of intrahepatic bile ducts
   - **Alagille syndrome**:
     - Paucity of intrahepatic bile ducts
     - Associated with Cong. Heart, vertebrae anomalies
     - Cornea anomalies & triangular face
   - **Progressive familial intrahepatic cholestasis (PFIC)**
   - **Benign recurrent cholestasis**
5. **Extrahepatic biliary atresia (EHBA)**
   - The cause
   - Associated with normal weight at birth
6. **Choledochal cyst**

**Consequences of cholestasis**

- Dark urine
- Jaundice
- Itchy skin
- Bradycardia
- Hepatomegaly
- Steatorrhea
- Clay-colored stool
Consequences of cholestasis

1. Decreased bile delivered to the intestine ➔
   - fat malabsorption
   - fat soluble vitamin deficiencies (A, D, E, K)
   - Pale or clay colored stool.

2. Retention of bile constituents ➔
   - jaundice Yellowish green discoloration of the skin & sclera
   - pruritis and Bradycardia (retained bile acids)
   - dark urine (retained bilirubin)
   - Progressive hepatomegaly and liver damage (by copper)

Clinical picture: Cholestasis should be suspected in any case of persistant neonatal jaundice beyond 2 weeks

1 - Discuss the consequence

2 - Manifestations of specific cause: e.g.
   - Marked hepatomegaly with adequate growth ➔ EHBA (➔ = suggest)
   - Low birth weight – Microcephaly – HSM ➔ congenital infection
   - Cataract ➔ Galactosemia or congenital rubella
   - Low birth weight or microcephaly ➔ congenital infections
   - abnormal facies, congenital heart, vertebral anomalies ➔ Alagille syndrome

3 - Picture of complications:
   - Failure to thrive
   - Cirrhosis in infancy
   - Portal hypertension and splenomegaly
   - Liver cell failure.

Steps of diagnosis of cholestasis:

a- Prove cholestasis by:
   - ↑↑ Bilirubin (Direct > 20% total).
   - ↑↑ ALT (liver specific), AST, Alkaline phosphase, γ–Glutamyl transferase
   - γ–Glutamyl transferase is normal in PFIC & in bile acid biosynthetic defect

b- assessment of liver function

c- Then do 5 steps to diagnose:
   1. Search for treatable conditions
      - Galactosemia: Reducing substance in urine or G1PUT assay in blood
      - Septicemia: Sepsis screen (CBC, ESR, CRP, blood culture).
      - Urinary tract infection: Urine analysis and culture.
   2. TORCH screening:
      - Total Ig M antibody: if > 20 mg/dl
      - Specific Ig M antibodies of TORCH agents is done accordingly
   3. Search for other metabolic conditions
      - Tyrosinemia: Succinyl acetone in urine.
      - Alpha one antitrypsin deficiency: enzyme level.
   4. Abdominal U/S:
      - May show Choledochal cyst
5. **Differentiation between Idiopathic hepatitis & Extra-hepatic biliary atresia:**

- **Percutaneous liver biopsy (most reliable):**
  - In *hepatitis*: Giant cell transformation.
  - In *atresia*: expansion of portal areas with fibrosis & bile duct proliferation

- **Radio-scanning (HIDA scan):** if dye didn't reach duodenum at all → extrahepatic biliary atresia.

### Management of cholestasis:

- **Replacement therapy**
  - ↑↑ fat soluble vitamins
  - Vit. K injection – oral vitamin A and E
  - ↑↑ Ca & Phosphorus and vit D
  - Fat in the form of medium chain triglycerides
    - N.B.: The best in infant with cholestasis is → predigested formula

- **Specific treatment:**
  - Sepsis: Antibiotics
  - Galactosemia: Lactose free milk
  - Kasai operation: (hepatic portoenterostomy) for EHBA
    - Best results before the age of 2 month
    - Post operative complications: cholangitis
  - Surgical removal of Choledochal cyst

- **symptomatic:**
  - Pruritis: bile acid binders as cholestyramine.
  - Varices: injection sclerotherapy
  - Hepatic encephalopathy: 10% glucose infusion, enema and oral neomycin

- **Liver transplantation:** this is the 1 indication in infancy
**Portal hypertension**

**Definition:** Portal venous pressure exceeds 12 mmHg (Normal: 5-10 mmHg)

**Causes:**

1. **Prehepatic:**
   - Congenital Portal vein obstruction
   - Portal vein thrombosis due [Umbilical sepsis - Umbilical vein catheterization]

2. **Hepatic:**
   - **Sinusoidal:** mention causes of Cirrhosis & cholestasis
   - **Presinusoidal:**
     - Bilharzial fibrosis
     - Congenital hepatic fibrosis
       - Present > 2 years with PHT
       - Diagnosis : liver biopsy
   - **Postsinusoidal:** veno-occlusive disease

3. **Posthepatic:** Budd-Chiari & Constrictive pericarditis

**Pathophysiology**

- Development of collaterals
  - Carrying the blood from the portal venous system to the systemic circulation.
  - Bleeding from the submucosal collaterals only;
    - (Esophageal varices), (gastric varices) and rectum (hemorrhoids)

**Clinical features:** 3 main characteristic findings:

1. **Collateral circulation:**
   - Hematemesis (due to esophageal varices) and earliest variable severity
   - Caput medusa: Dilated anterior abdominal wall veins

2. **Splenomegaly:**
   - Very early and evident in prehepatic and hepatic causes
   - Hypersplenism may occur and results in thrombocytopenia or pancytopenia

3. **Ascites:**
   - Evident in advanced cases
   - Early in post-sinusoidal portal hypertension.
Investigations
- **Upper GIT endoscopy** for detection of esophageal varices
- **Abdominal ultrasonography** and Doppler ultrasonography:
  - Demonstrate the direction of flow within the portal system
  - the patency of the portal vein and
  - Presence of portosystemic collaterals.
- **CT angiography** and **MR venography** (demonstrate vessel patency)
- **Liver function test**
- **Investigation for the cause**
  - Hepatitis markers
  - Autoimmune screening
  - TMS- sweet chloride test
  - Liver biopsy

Management:

1. **Emergency treatment of bleeding varices:**
   - Hospitalization.
   - IV fluid resuscitation & blood transfusion.
   - H2 blockers as ranitidine.
   - If bleeding persists:
     - Vasopressin infusion.
     - Emergency Sclerotherapy
     - Transjugular intrahepatic porto-systemic shunt.
     - Surgical portosystemic shunts as portocaval shunts.

2. **Prevention of bleeding:**
   - Avoid aspirin and hard food.
   - Beta blockers as propranolol (reduces portal venous pressure).
   - Prophylactic sclerotherapy or band ligation.
   - Portosystemic shunts
   - Liver transplantation.

Cirrhosis

**Definition:** Irreversible damage of liver architecture with fibrosis and nodule formation.

**Causes:**

1. **Causes of chronic hepatitis**
2. Biliary cirrhosis mention causes
3. Congestive: Constrictive pericarditis and Budd Chiari syndrom