

Liver disease in children

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Objectives

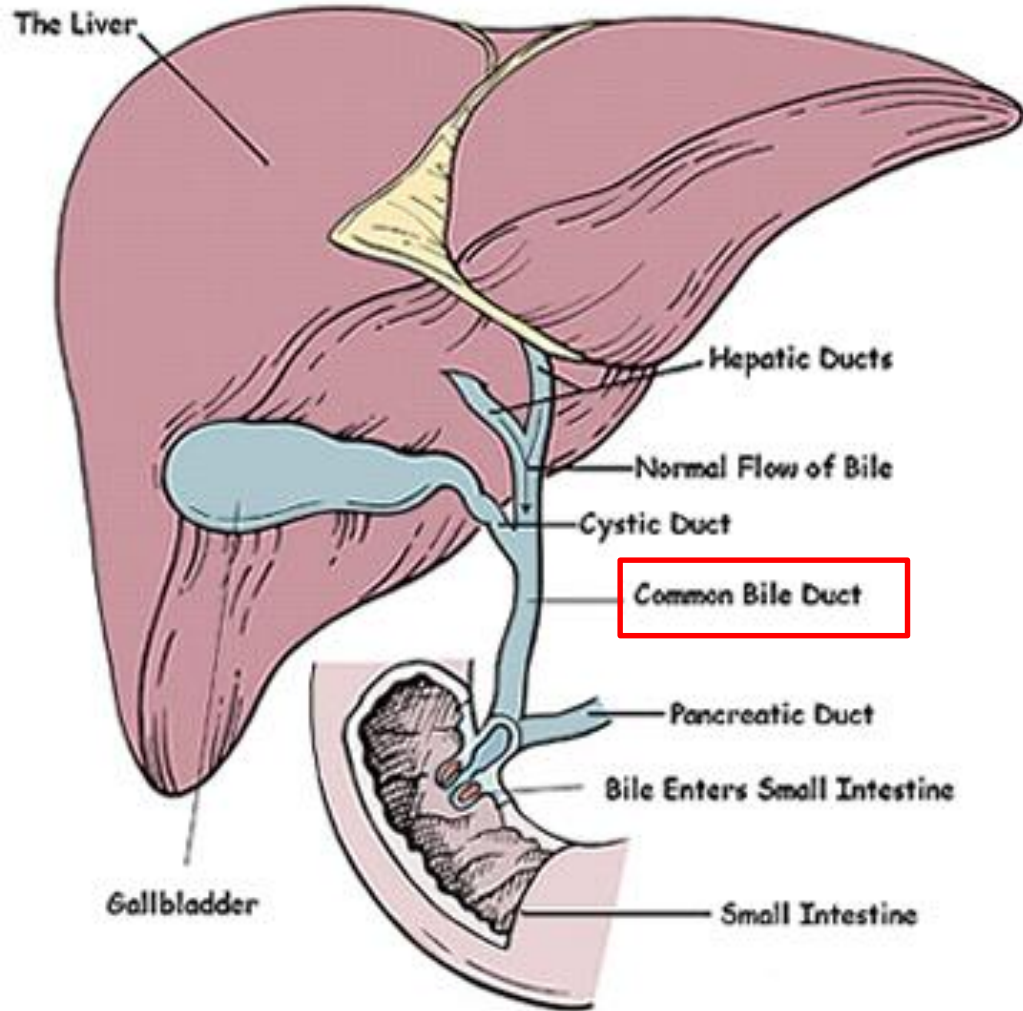
- To understand the anatomy & physiology of liver & biliary tree
- To be able to read & interpret the basics of liver function tests
- To be able to recognize the variable presentations of acute & chronic liver disease

- To know the most common conditions causing neonatal liver diseases & chronic liver diseases in children
- To know how to diagnose these conditions appropriately

PART - 1

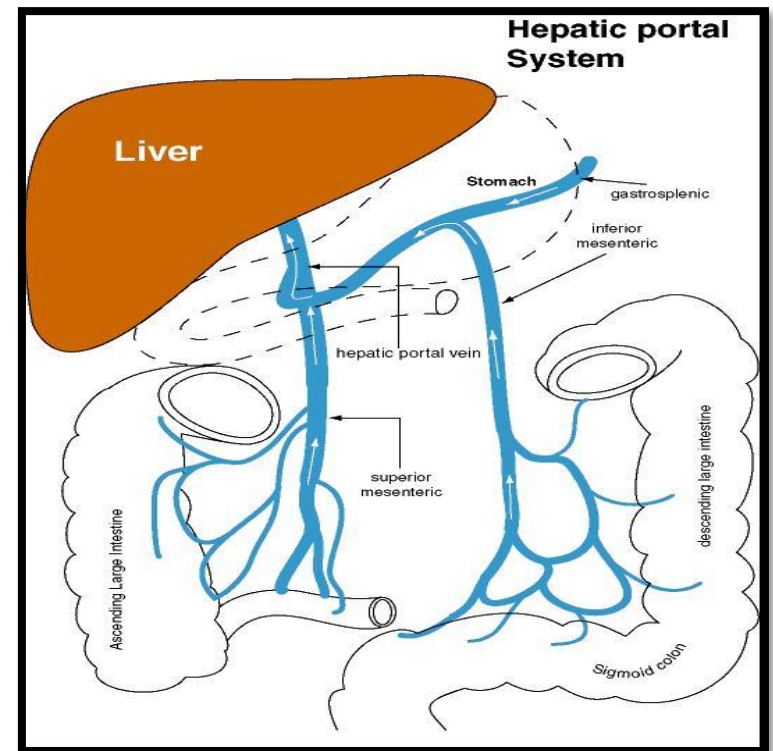
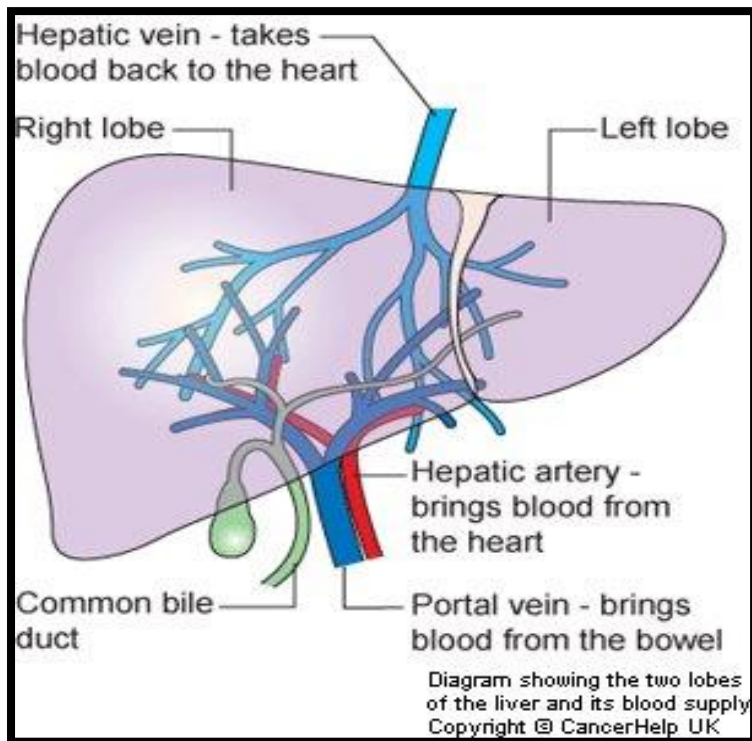
NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

Liver anatomy

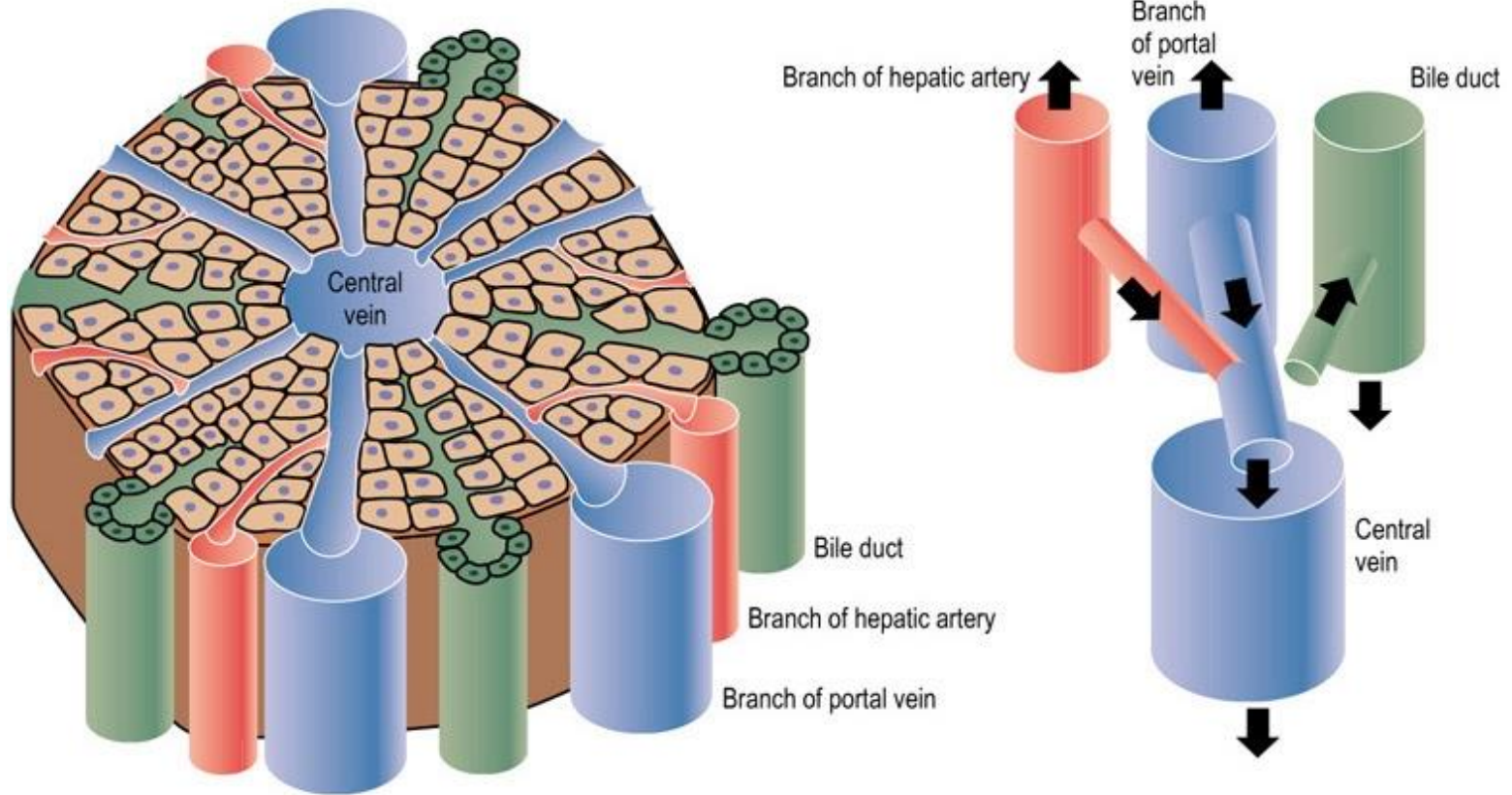


Liver blood supply

- Liver has **dual (bouble) Blood supply** resources ;
 - 70% from **portal vein (nutrients)**
 - 30% from **Hepatic artery (oxygenated blood)**



Liver Histology



Liver FUNCTIONS

Synthetic Function

- 1- **Glucose**
- 2- **Plasma proteins:**
(albumin, globulins, Clotting factors)
- 3- **Lipids:** cholesterol and lipoproteins
- 4- **Bile salts**

Detoxification and excretion

- 1- **Bilirubin**
- 2- **Ammonia** to urea (urea cycle)
- 3- **Drug metabolites**
- 4- **Cholesterol**

Storage Function

- 1- **Glucose** → **Glycogen**
- 2- **Vitamins** A, D, E, K and B₁₂

What are the liver function markers?

Liver enzymes # LFTs

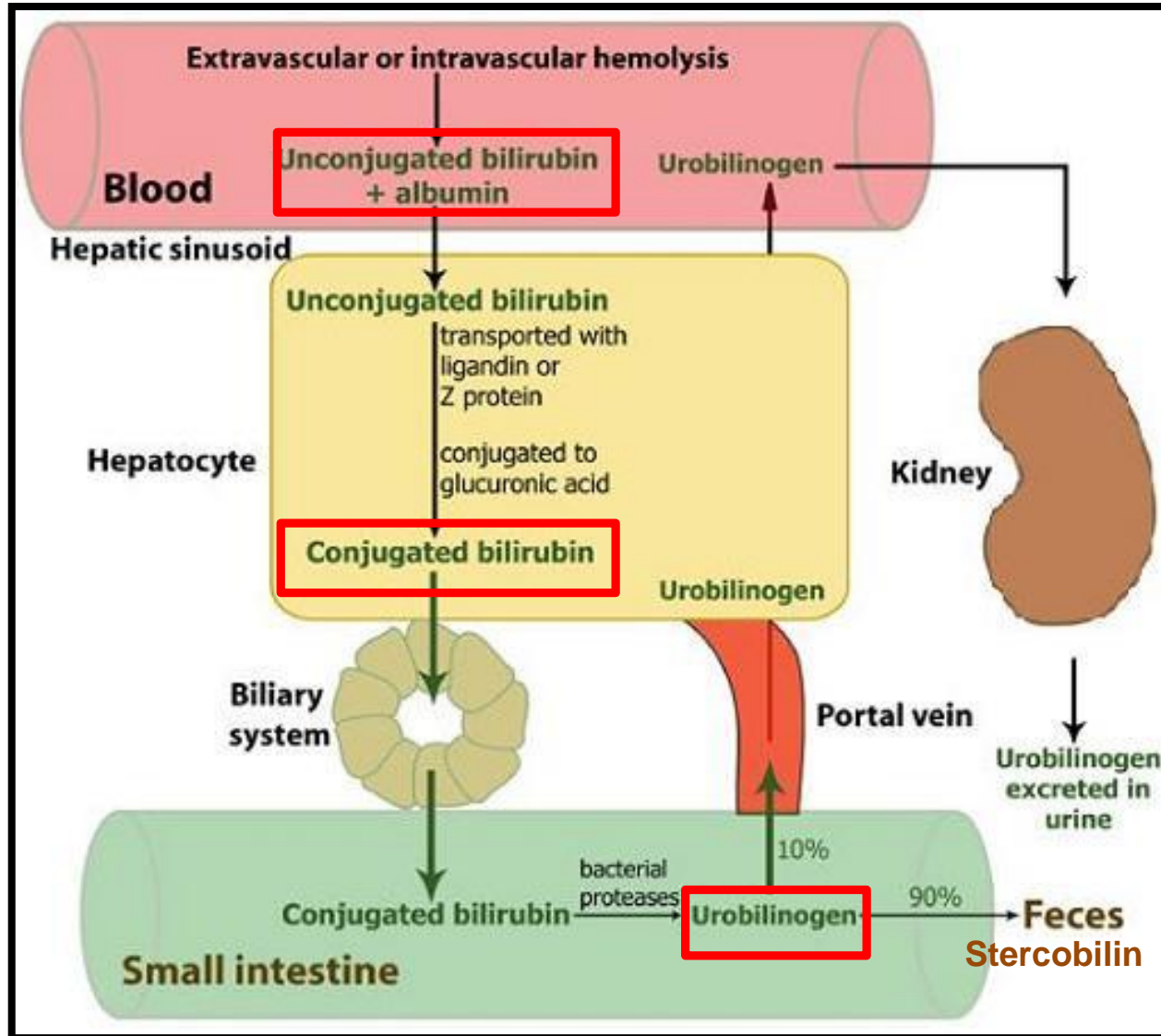
- Enzymatic markers:

- ALT (more specific)
- AST
- ALP
- GGT (more specific)

- Synthetic function markers:

- Glucose
- Bilirubin
- Bile acids
- Albumin, Globulins
- Clotting factors (PT & PTT)
- Urea (from NH₃ & AAs)

Bilirubin metabolism



Hyperbilirubinemia: (important numbers)

- Hyperbilirubinemia (HB) **biochemically** = **TSB > 1.5 mg/dl** (26 mmol/l)
- Jaundice become **clinically** evident if total **SBL > 5 mg/dl** (86 mmol/l)
- Conjugated HB: if **cong. Billi. > 20 %** of the total Bili (mcq)

Hyperbilirubinemia

- Conjugated/Direct HB \Leftrightarrow Liver disease
- Unconjugated/Indirect HB is mostly non-liver related (RBC hemolysis-- Muscle disease)

EXCEPTIONS:

- Criglar Najjar syndrome
- Gilbert syndrome

Causes of un-conjugated HB

(MCQs)

Haemolysis ;

- **COOMB +ve:**
 - ABO incompt., Rh incompt
 - Autoimmune
 - Drug-induced HA
- **COOMB - ve;**
 - RBC membrane defects-
Hbpathy- Enzyme defects
 - HUS

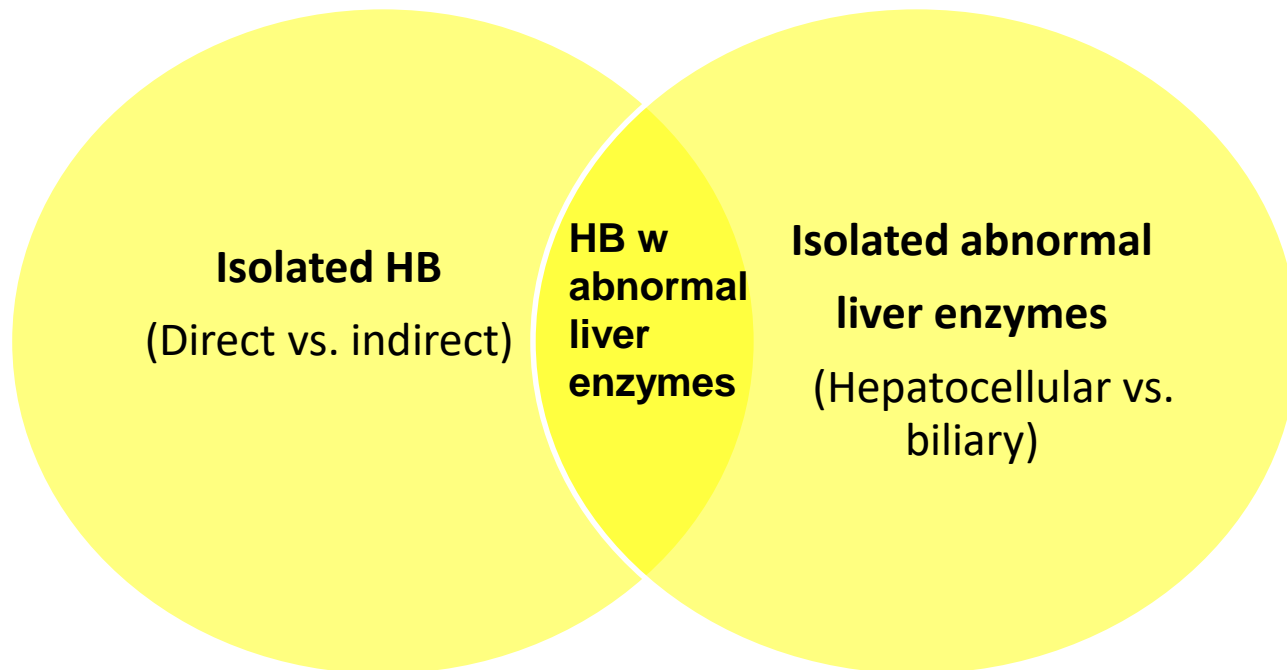
Non- haemolysis;

- 1- Breast feeding/Milk
Jaundice
- 2- **Criglar Najjar syndrome**
- 3- hypothyroidism

- 4- **Gilbert syndrome**

Biochemical Patterns of liver diseases

- Isolated **Hyperbilirubinemia** (HB)
- Isolated **abnormal liver enzymes** (w/t HB)
- **Both** (Hyperbilirubinemia with abnormal liver enzymes)



Isolated Hyperbilirubinemia

Disease	Defect	Manifestations	TREATMENT
Gilbert's syndrome	Mutation in UGT1A1 (< 30% of the normal activity)	Mild jaundice during stress	None
Crigler-Najjar syndrome type 1	Mutation in UGT1A1 (absent activity)	Sever jaundice (risk for kernicterus)	PhytoTx Exchange Tf Liver Tp
Crigler-Najjar syndrome type 2	Mutation in UGT1A1 (< 10% of the normal activity)	Mild-mod jaundice	Phenobarbitone
Direct HB			
Dubin-Johnson syndrome	MRP2 receptor mutation (impair transport process across canalicular membrane)	Neonatal cholestasis – no symptoms	None
Rotor syndrome	OTP1B1 & OTP1B3 mutation (affect reuptake of cong. Billi by hepatocytes)	Neonatal cholestasis – no symptoms	None

Patterns for liver diseases:

1) *Cholestatic or obstructive bile duct injury*

GGT /ALP > AST/ALT

2) *Hepatocellular or liver cell injury:*

ALT/AST > GGT/ALP

3) **Mixed: Mostly**

- There is often considerable overlap between injury types in a patient who has liver disease.

QUESTIONS
FROM PART 1

PART-2

Liver disease in children

Liver disease in children

- **Variable : age dependant**
 - **Infants:** Biliary atresia (BA), Neonatal hepatitis, metabolic liver disease, genetic disorders (progressive familial intrahepatic cholestasis (PFIC))
 - **Older children = adults liver diseases:**
Viral Hepatitis, Wilson disease, Auto-immune hepatitis, ect...
- **The main presenting symptoms of liver disease is jaundice**
- **Any jaundice after 2 weeks of age should be investigated (MCQ)**

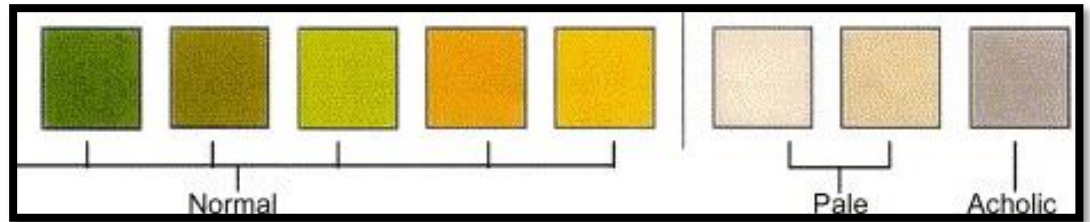
Cholestatic liver disease

- **Cholestasis → chole= bile Stasis=stagnation**
- The obstruction of bile flow either:
 - **Mechanical block** (biliary atresia, stones...) or
 - **Functional block** (cellular **receptor & transporter** levels):eg: progressive familial intrahepatic cholestasis (PFIC)
- **Cholestasis is characterized by an accumulation of compounds that cannot be excreted through the bile**
 - Conjugated/direct bilirubin → jaundice (**Cholestasis # jaundice**)
 - Enzymes (GGT/ALP>ALT/AST) → high liver enzymes in serum
 - Bile salts → itchiness
 - Cholestrol → xanthomas

Presentation of cholestasis

- **Jaundice** (accumulation of conjugated bilirubin)
- **Pale stool (Acholic stool)... Why?? (MCQ)**
- **Dark and foamy urine** (bile salts in the urine)
- **Pruritis** (accumulation of bile salts under the skin)
- **Xanthomas depositions** (accumulation of cholesterol in the skin)
- **Hepatomegaly +/- Splenomegaly** (Portal HTN, Storage disease, infiltrative process)
- **Failure to thrive (FTT)/** poor weight gain
- **Incidental lab finding**

Signs of cholestatic liver disease



Evaluation of infants with **cholestatic** **liver disease**

- **STEP 1: Confirm the presence of cholestasis**
(Clinically: jaundice, acholic stool, pruritis, & lab: direct hyperbilli)
- **STEP 2: Rule out surgical obstruction** such as Biliary atresia, Choledocal cyst and GB stones (Abdm US)
- **STEP 3: Investigate the treatable medical conditions:**
 - Infections: UTI, TORCH infections
 - Endocrine: hypothyrodism, panhypopituitarism
 - Metabolic disorders (Galactosemia, Tyrosenemia)
- **STEP 4: Further studies for other causes (genetic/metabolic)**

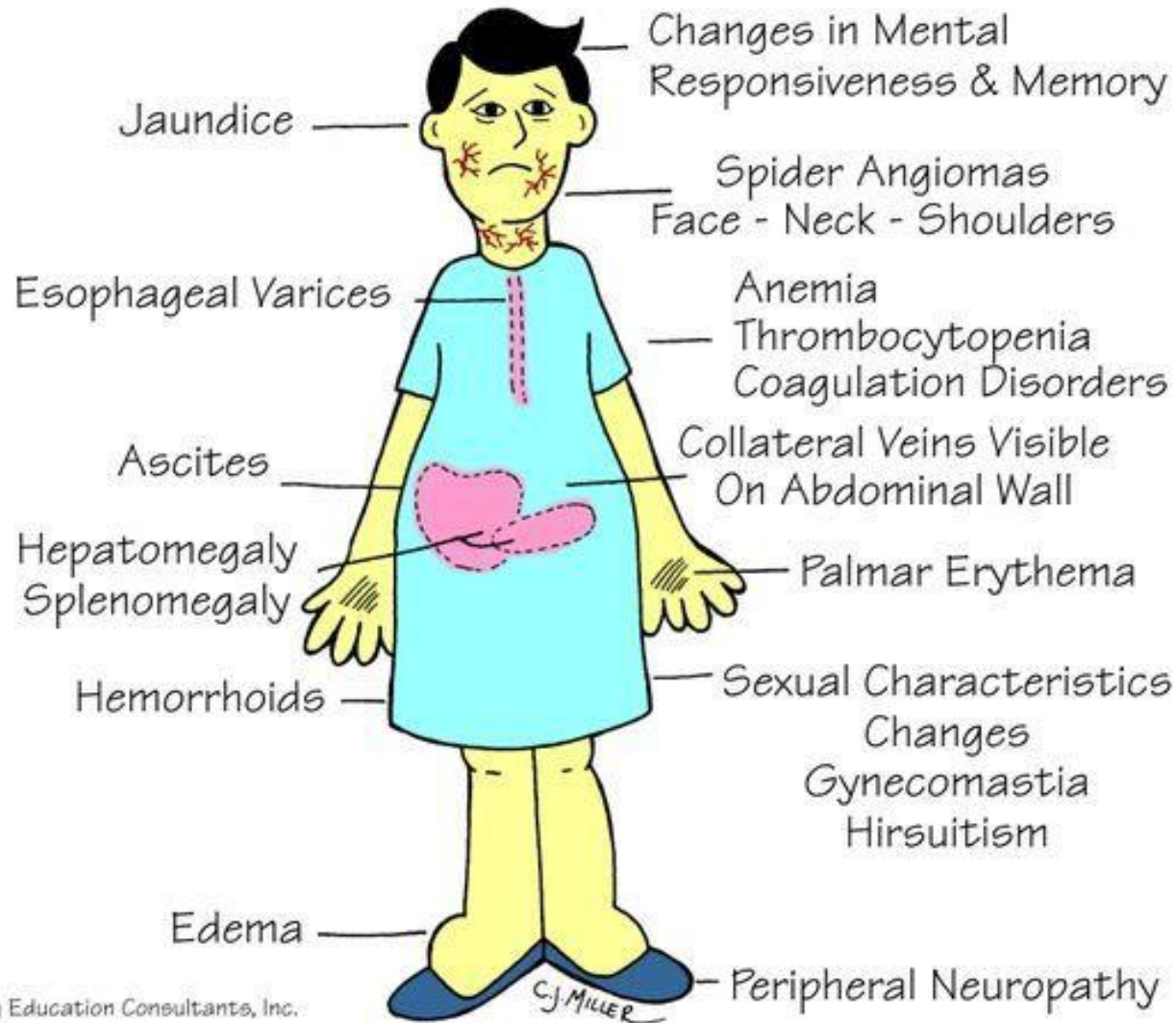
Hepato-cellular liver disease

- Necrosis of hepatocytes following a viral, ischemic or toxic insult to the liver will cause primarily an elevation of enzymes found within the hepatocyte (ALT and AST)
- In hepatocellular disease, the serum levels of GGT and AP do not rise to the same degree as the aminotransferases (in general)

Chronic hepatitis

- **Definition:**
 - an inflammatory condition of the liver in which the biochemical and histologic abnormalities persist for more than 6 months from any disease.
- **Chronic hepatitis in children can be caused by:** viral infection (Hep B & C); autoimmune process; hepatotoxic drugs; or metabolic, or systemic disorders
- Can progress to CLD if the primary disease not treated well

CIRRHOSIS: LATER CLINICAL MANIFESTATIONS



Causes of liver disease in *neonates & infants (both types)*

- Cholestatic disorders

- Biliary atresia
- Choledochal cyst
- Paucity of intrahepatic bile ducts (eg, Alagille syndrome)
- Progressive familial intrahepatic cholestasis syndromes (Byler disease and syndrome)
- Benign recurrent intrahepatic cholestasis
- Caroli disease and syndrome
- Inspissated bile (S/P hemolytic disease)
- Cholelithiasis

- Idiopathic neonatal hepatitis and mimickers

- Cystic fibrosis
- Alpha 1-antitrypsin deficiency
- Hypopituitarism/hypothyroidism
- Neonatal iron storage disease

- Viral hepatitis or other infectious diseases in the neonate

- Cytomegalovirus
- Herpes simplex virus/herpes zoster virus/human herpesvirus 6
- Epstein-Barr virus
- Parvovirus B19
- Rubella
- Reovirus—type 3
- Adenovirus
- Enterovirus
- Bacterial sepsis/urinary tract infection
- Syphilis
- Tuberculosis
- Toxoplasmosis

Causes of liver disease in neonates & infants

- Metabolic disease
 - Disorders of peroxisomal function (Zellweger syndrome)
 - Disorders of bile acid metabolism
 - Disorders of urea cycle (arginase deficiency)
 - Disorders of amino acid metabolism (tyrosinemia)
 - Disorders of lipid metabolism (Niemann-Pick type C/Gaucher/Wolman)
 - Disorders of carbohydrate metabolism (galactosemia, fructosemia, type IV glycogen storage disease)

- Toxic/pharmacologic injury (eg, acetaminophen, total parenteral nutrition, hypervitaminosis A)

- Tumors (intra- and extrahepatic)

QUESTIONS from part 2

PART-3

SPECIFIC LIVER DISEASES IN INFANTS

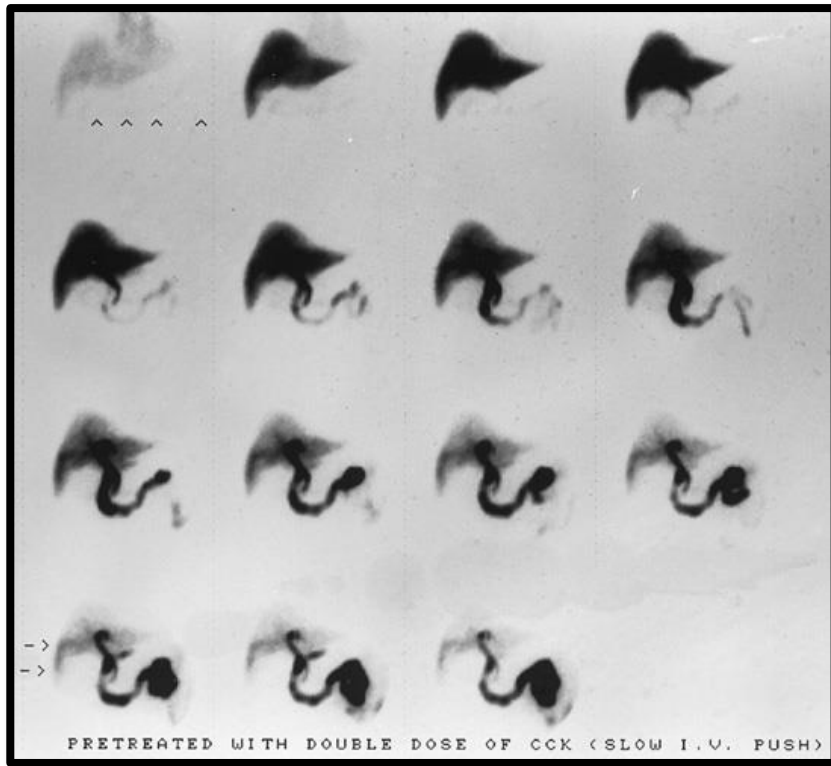
Biliary Atresia (BA)

- Biliary atresia is an obstructive disease of the **biliary tree** (mainly extra-hepatic) secondary to idiopathic inflammatory/autoimmune process??
- It leads to gradual fibrosis and ultimate obliteration of the biliary tract → biliary cirrhosis → liver failure → **infant death within 2 years if not treated (surgery or liver transplantation)**
- **The most frequent indication worldwide for liver transplantation among infants and children (NOT in KSA)**

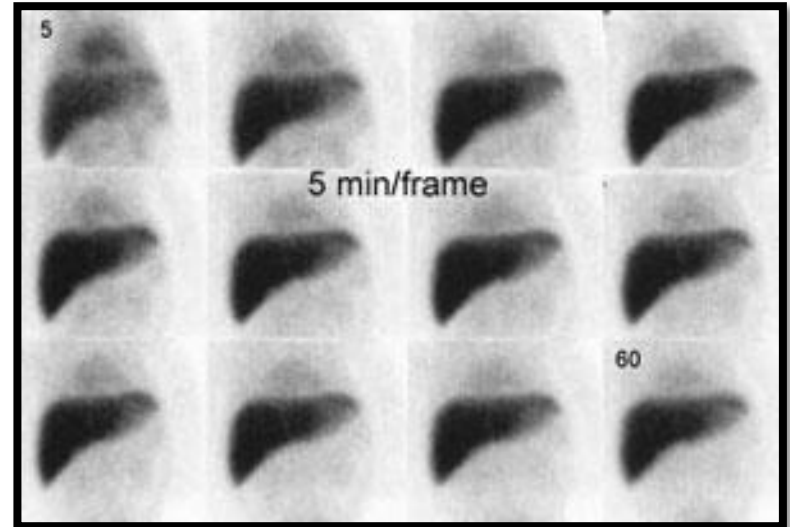
BA - Diagnosis

- **Clinical presentation:**
 - It presents with **signs of cholestasis** (jaundice, acholic stool, pruritis, FTT) in the **first 2-6 weeks of life (MCQ)**
- **Abdominal US:** rule out other causes of biliary obstruction (choledochal cyst, GB stones...)
- **Hepato-biliary scintigraphy = nuclear scan (HIDA scan):**
 - shows good uptake of tracer and then NO excretion into the intestine, even 24 hours later (next slide)

Hepato-biliary scintigraphy (HIDA scan)



NORMAL HIDA SCAN

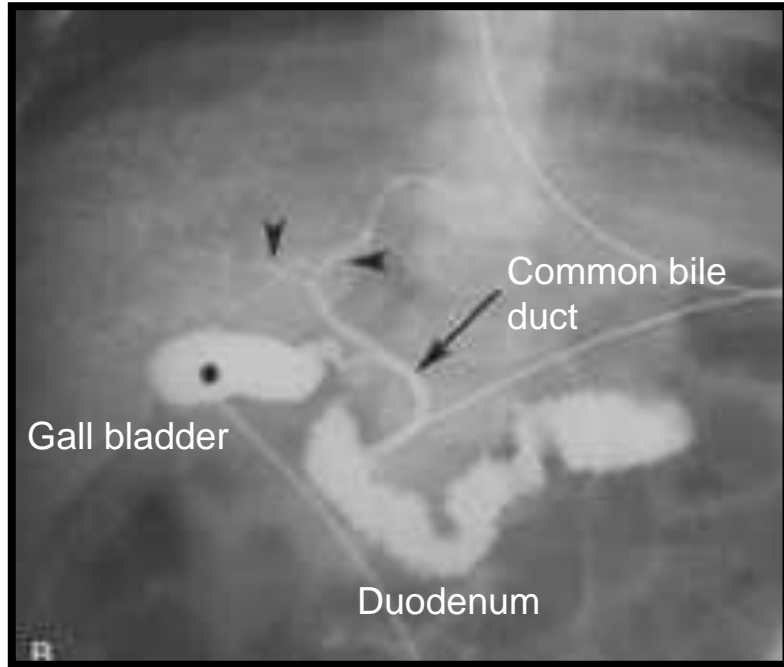


HIDA scan in BA patient

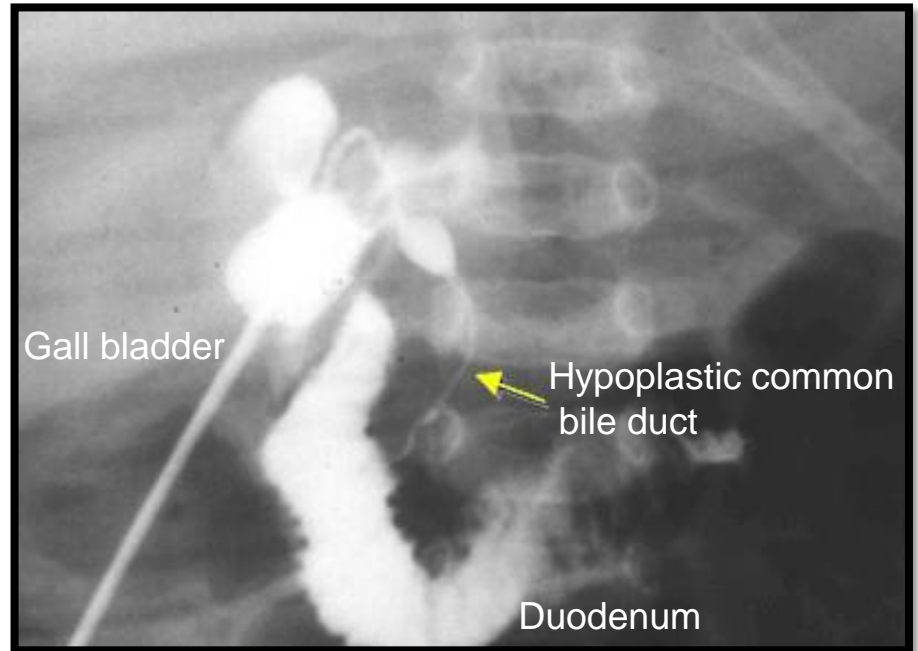
BA - Diagnosis

- **A liver biopsy:**
 - confirms the diagnosis by revealing characteristic findings (proliferation of the interlobular bile ducts, periportal fibrosis, and bile plugs in canaliculi and ductules)
- Definitive diagnosis is confirmed by **Intra-operative cholangiogram**

Definitive diagnosis is confirmed by
Intra-operative cholangiogram



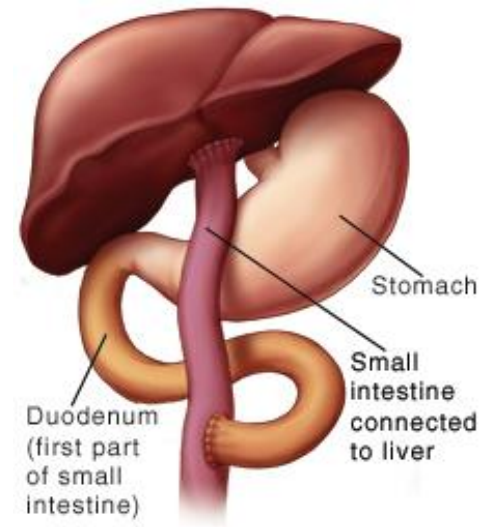
Normal study



**Abnormal study
(hypoplastic common bile duct)**

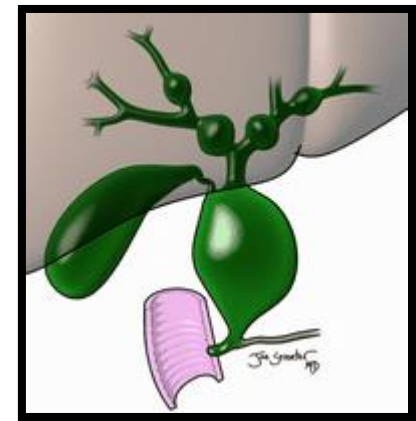
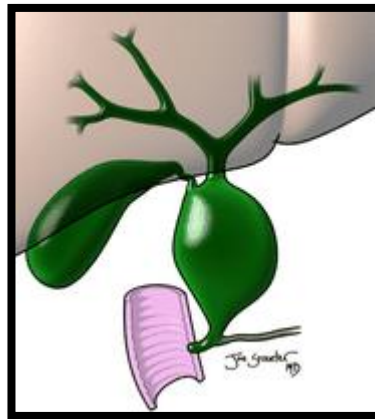
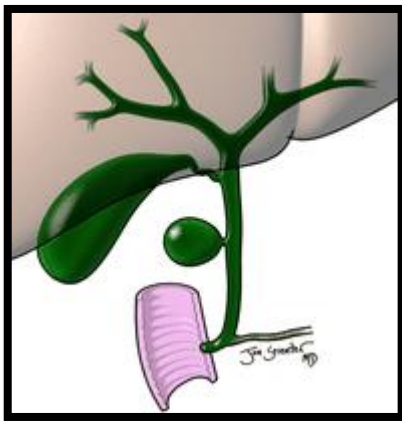
BA Management

- **Surgical correction (Kasai procedure or porto-entero-stomy) :**
- Should be done before 2 months of age (MCQ)
 - after this age, there is increased risk of fibrosis & subsequent cirrhosis → decrease the chance for surgery success)
- **Liver transplantation if:**
 - Kasai failed, or
 - Late presentation (> 3 months) or
 - Decompensated liver disease



Choledocal cyst

- Cystic dilatation of the biliary tree at different levels → **obstructive picture**
- Present with cholestasis picture, abdominal mass or asymptomatic, biliary stones or biliary carcinoma in adults



- Treatment: surgical excision

Alpha-1 Antitrypsin deficiency

- A-1 AT is a protease inhibitor (inhibit elastase, trypsin) → protect lung from neutrophil elastase destruction
- **A-1 AT deficiency cause:**
 - Liver disease (children or adults)
 - Emphysema lung disease (mainly seen in adults)
- **AR disease** (rare in our community)
 - **Pi MM → Pi ZZ** → form abnormal A-1 AT protein → **failed excretion from liver (trapped)** → cholestatic liver disease

Alpha-1 Antitrypsin deficiency

- **Dx:**
 - A-1 AT level, phenotyping (pi ZZ) and
 - confirmed with Liver biopsy (seen in special stain)
 - Genetics
- **Treatment: supportive**
- **Prognosis:** varies (improve over time> chronic liver disease)

Neonatal Hepatitis

- “Idiopathic” neonatal hepatitis = an **aetiology has not been identified**
- The list **gets smaller overtime** (new advancement in diagnostic modalities = more genetic & metabolic causes are discovered daily)
- Management of these infants involves supportive measures till specific cause found

?? Questions PART 3

Part 4

SPECIFIC LIVER DISEASES IN OLDER CHILDREN

Liver disease in older children = adults !!

- **Infectious** (Viral, Bacterial, Protozoal)
- **Toxic/medications** (drugs, TPN)
- **Ischemia** (CR arrest, hypotention)
- **Metabolic disorders** (CHO, FAT, Amino Acids)
- **Autoimmune: AIH**
- **Genetics; Wilson disease**
- **Vascular** (thrombosis)
- **Infiltrative/Malignancy** (leukemia, primary liver tumours)

Acute hepatitis

- Five primarily viruses: hepatitis A, B, C, D, and E
- The clinical presentation of viral hepatitis varies with the pathogen (**hepato-cellular injury** → mixed)
- **HEPATITIS A: (MCQs)**
- ***Presentation:***
 - ***flu-like illness*** , Anorexia, fever, vomiting, abdominal pain, darkening of the urine, **following ingestion of contaminated food or contact with infected patient (oral-fecal route)**
- Hepatitis A is often **an-icteric (no jaundice) in young children (<5 y)** and frequently is unrecognized

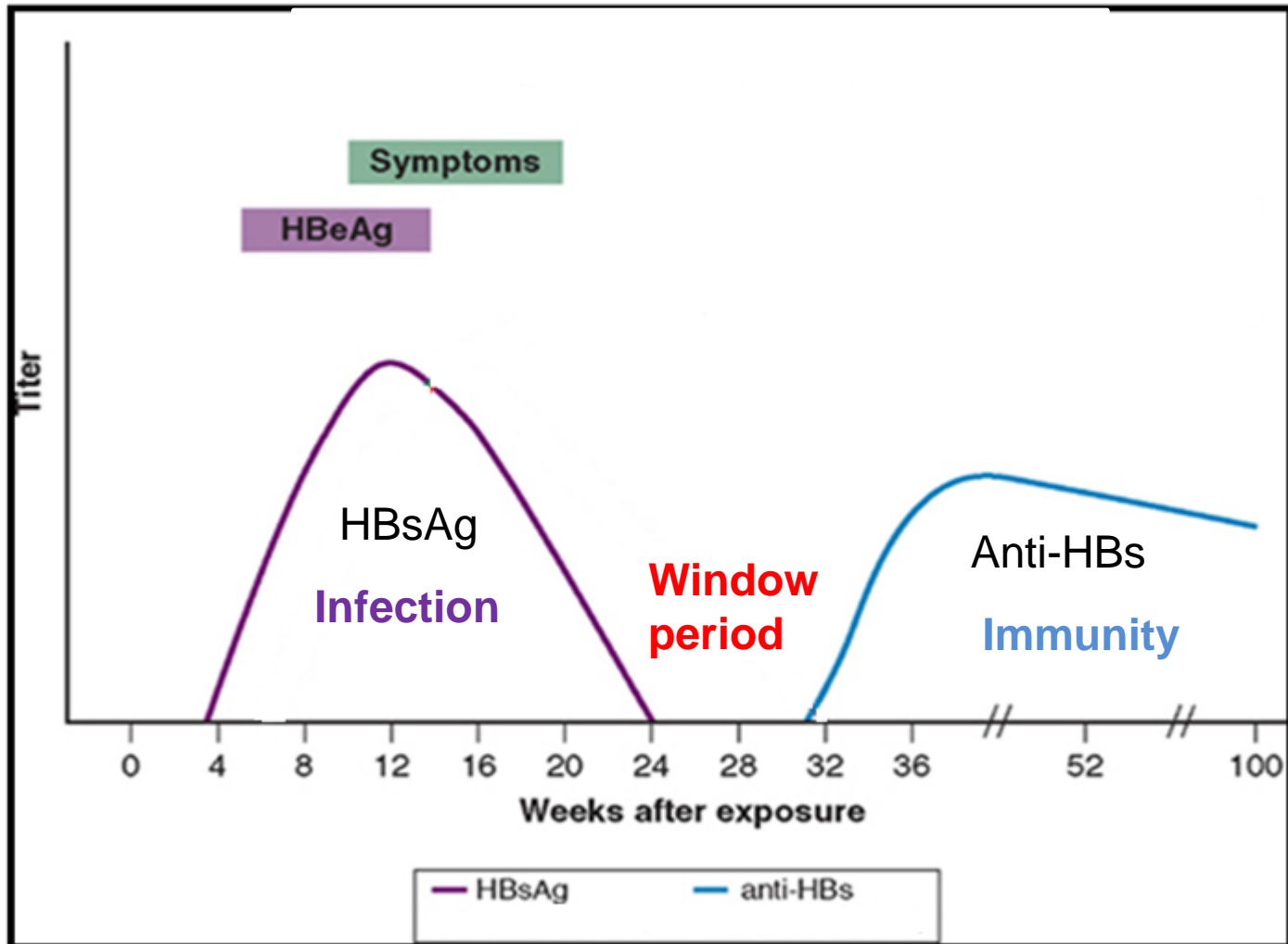
HEPATITIS A

- **Diagnosis** of acute infection is based on the presence of anti-HAV IgM antibody in serum (MCQ)
- The disease typically is self-limited in children and often is clinically not clear
- No chronic carrier state is identified (full recovery or rarely death from fulminant liver failure)
- **Treatment** is supportive (IVF, Antipyretics)
- **Prevention:** Hep. A vaccine: 2 doses (18 ms & 24 months)

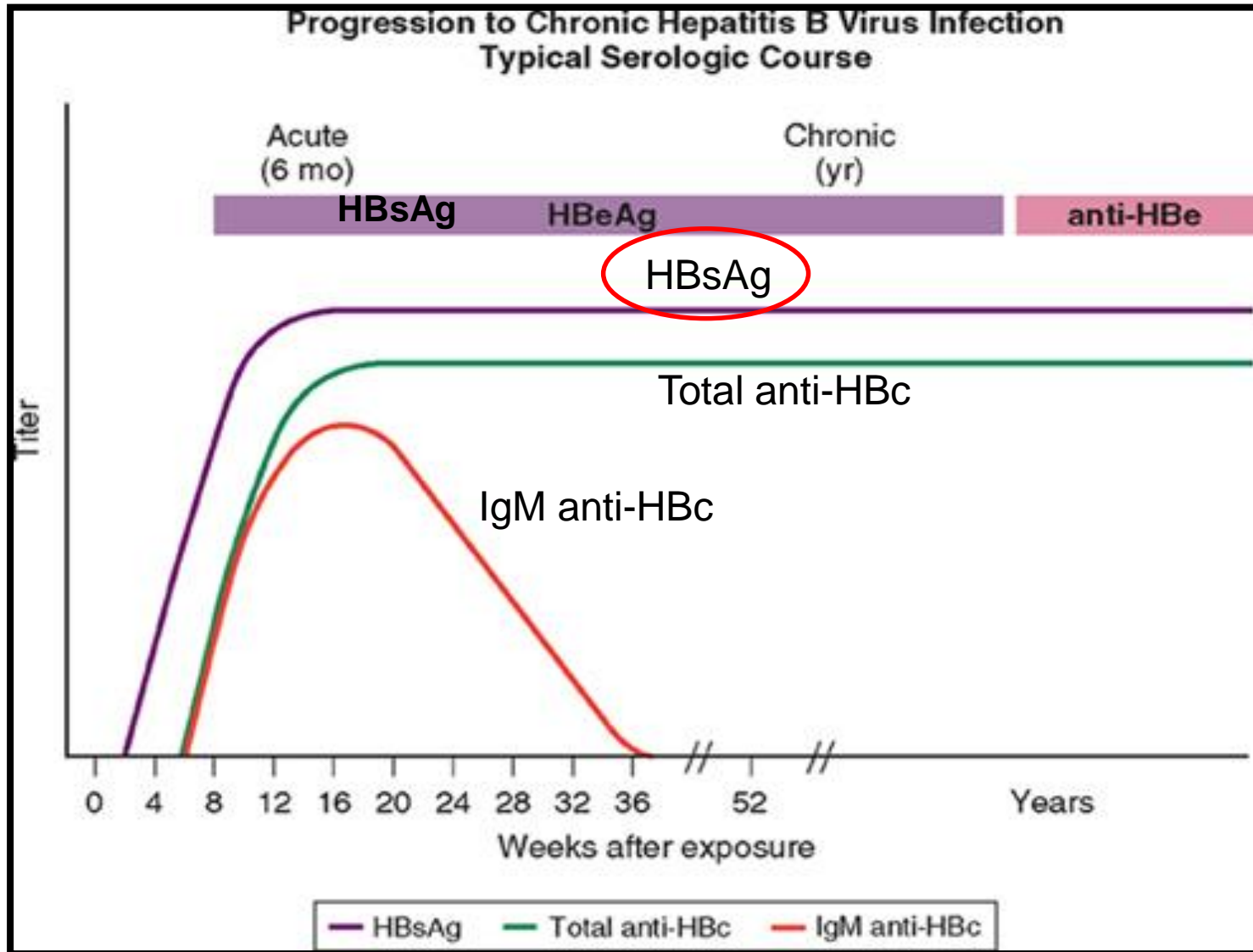
Hepatitis B

- Hepatitis B virus (HBV) infection can cause both acute and chronic hepatitis
- It can progress to cause **cirrhosis and hepatocellular carcinoma** if not treated (take long time to happen)
- **Risk of transmission:** primarily vertical (mother to baby) in children or via contaminated blood + other risk factors..
- **Diagnosis:** Hepatitis B surface antigen (HBsAg)
- **Chronic HBV infection** is associated with the persistence of HBsAg and HBV DNA for > 6 moths

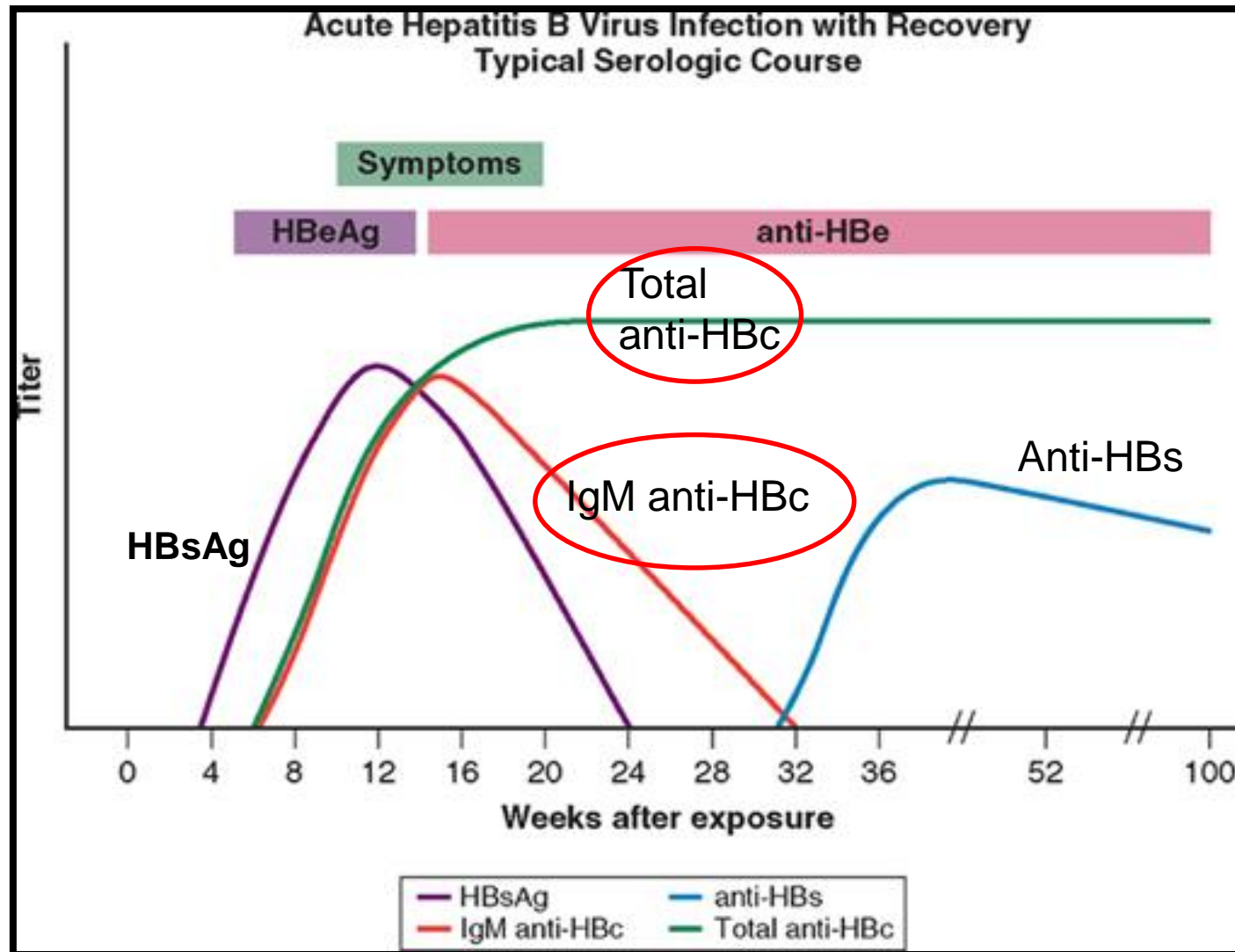
HBV serology markers



Chronic hepatitis



HBV serology markers.. recovery



Hepatitis B serological markers

HBsAg	negative	Susceptible
anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Immune due to natural infection
anti-HBc	positive	
anti-HBs	positive	
HBsAg	negative	Immune due to hepatitis B vaccination
anti-HBc	negative	
anti-HBs	positive	
HBsAg	positive	Acutely infected
anti-HBc	positive	
IgM anti-HBc	positive	
anti-HBs	negative	
HBsAg	positive	Chronically infected
anti-HBc	positive	
IgM anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection
anti-HBc	positive	
anti-HBs	negative	

Treatment

- **Prevention:**
- **newborn of Hep BsAg-positive mothers (MCQ):**
 - **Passive immunization: Hep. B Immunoglobulins** (within 12 hrs of birth)
 - **Active immunization: Hep. B Vaccine after birth** (within 7 days after birth, then at 1 month & 6 months)
- **Rx for older children: antiviral meds**
 - ??? Wait & observe (spontaneous recovery, new better antiviral meds with less side effects)

Hepatitis C

- Hepatitis C virus (HCV) causes acute hepatitis, which progresses to chronic disease (**End-stage liver disease can occur in up to 10 %**)
- Risk of transmission similar to hepatitis B
- **Diagnosis** is based on the detection of
 - persistently elevated anti-HCV antibodies (above 18 ms of age)
 - **confirmed** by PCR for HCV RNA-active infection

Hepatitis C

- **Treatment:**
 - Spontaneous viral clearance from acute infections can occur in pediatrics (15-56%)
- antiviral Rx (new generation, > 95% effective)
- **Prophylaxis:** no vaccine yet

Hepatitis D

- Hepatitis D virus (HDV) infection occurs only in patients who have HBV infection
- Associated primarily with intravenous drug abuse
- HDV usually aggravates liver disease in a patient who has hepatitis B and always should be considered in those who have particularly aggressive HBV disease

Hepatitis E

- Hepatitis E virus (HEV) occurs in epidemics in parts of the world that have poor sanitary conditions
- It can be a particularly devastating disease in pregnant women

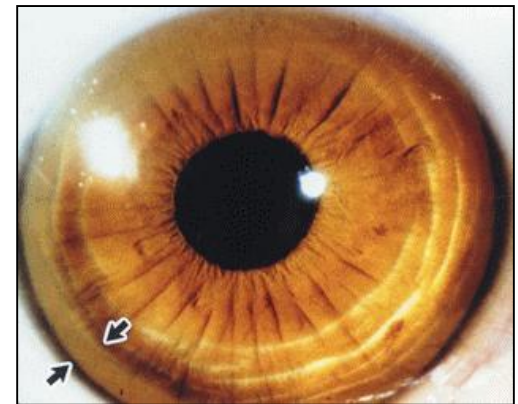
Viral hepatitis.. summary

	Hepatitis A virus (HAV)	Hepatitis B virus (HBV)	Hepatitis C virus (HCV)	Hepatitis D virus (HDV)	Hepatitis E virus (HEV)
Viral genome	RNA	DNA	RNA	RNA	RNA
Transmission	Faecal-oral route	Blood and other body fluids	Blood	Blood and other body fluids	Faecal-oral route
Incubation period	14–28 days	30–180 days	14 days –6 months	HDV requires HBV for replication	14–70 days
Diagnosis	<ul style="list-style-type: none"> • Anti-HAV-specific AB • HAV RNA 	<ul style="list-style-type: none"> • HBV surface protein • Anti-HBV-specific AB 	<ul style="list-style-type: none"> • Anti-HCV-specific AB • HCV RNA 	<ul style="list-style-type: none"> • Anti-HDV-specific AB • HDV RNA 	<ul style="list-style-type: none"> • Anti-HEV-specific AB • HEV RNA
Possible chronic infection	No	Yes	Yes	Yes	Yes
Vaccine	Yes	Yes	No	No	Yes (in China only)

AB, antibody; DNA, deoxyribonucleic acid; RNA, ribonucleic acid

Wilson disease (a must to know)

- **AR** disorder
- caused by a defect in biliary copper excretion
- **Excessive copper accumulation (multi-systems):**
 - **liver** → leads to cirrhosis
 - **Other organs:** cornea, kidneys, and brain, resulting in extra-hepatic manifestations of the disease
- Wilson disease **SHOULD** be included in **the differential diagnosis of any child who presents with liver disease, neurologic abnormalities, behavioural changes (treatable condition)**



Wilson disease

- Wilson disease may present as ***fulminant hepatic failure***, usually in association with a ***hemolytic crisis*** due to the toxic effect of copper on red blood cells.
- **Definitive diagnosis** requires evaluation of:
 - 24-hour urinary copper excretion **and**
 - copper quantification in liver tissue obtained by biopsy
 - Genetic test (useful in asymptomatic children of 1st degree relatives)
- **Therapy** is **chelating** therapy of the copper with **penicillamine**, which allows for its excretion into the urine (early diagnosis = better prognosis)

AIH

- AIH is a hepatic inflammation associated with the presence of circulating autoantibodies against liver cells in the absence of other recognized causes of liver disease
- Other autoimmune diseases may coexist, including: thyroiditis, DM
- **Dx:**
 - High transaminases +
 - High autoimmune markers (anti SMA, KLM)
 - High serum gamma globulin concentrations
 - Liver biopsy
- Rx: Immunosuppressive medications e.g.: steroids....

Ischemic hepatitis

- Ischemic hepatitis results from **shock (eg, dehydration), asphyxia, cardio-respiratory arrest, or seizures.**
- The disorder is due to hypotension/hypoperfusion to the liver
- **Typically, aminotransaminases are elevated in the absence of other markers of severe liver disease.**
- Ischemic hepatitis may resemble infectious hepatitis, but it is distinguished easily by rapidly decreasing aminotransaminases levels in the days following the initial insult without increasing coagulopathy or hyperbilirubinemia.

Infiltrative disorders

- **Infiltrative disorders** of the liver are observed with leukemia, lymphoma, and neuroblastoma (*more common than primary liver tumors*)
- **Primary liver tumors:** Hepatoblastoma, hepatocarcinoma, and hemangioendothelioma
- **Presentation:** hepatomegaly or abdominal distension or mass
- Serum alpha-fetoprotein levels usually are elevated.
- Dx by CT scan or MRI
- Surgical excision of a solitary tumor or radiation/chemotherapy is the treatment of choice.

THE END

QUESTIONS

TABLE 6. Miscellaneous Physical Findings Associated With Liver Disease

Infants
• Microcephaly: congenital cytomegalovirus, rubella, toxoplasmosis
• Characteristic facies: arteriohepatic dysplasia (Alagille syndrome)
• Cataracts: galactosemia
• Retinal pigmentation and posterior embryotoxon: Alagille syndrome
• Abnormal auscultation of lungs: cystic fibrosis
• Neuromuscular abnormalities (tremors, flaccidity): lipid storage disease, Wilson disease, disorders of oxidative phosphorylation

Children
• Pruritus: chronic cholestasis
• Hemangiomas: hemangiomatosis of the liver
• Kayser-Fleischer rings: Wilson disease
• Glossitis: cirrhosis
• Enlarged kidneys: congenital hepatic fibrosis or polycystic disease
• Arthritis and erythema nodosum: liver disease with chronic inflammatory bowel disease
• Arthritis, acne, fatigue: autoimmune hepatitis