Liver disease in children

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Objectives

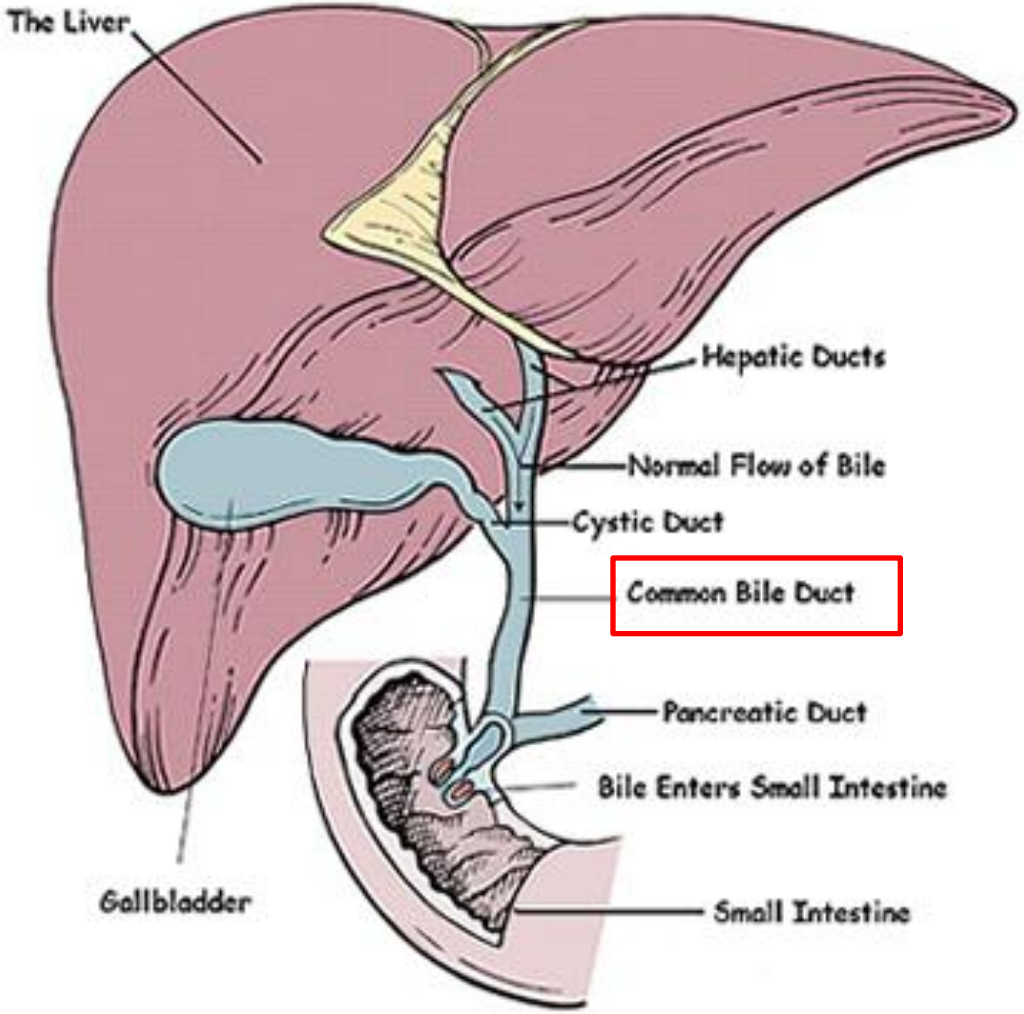
- To understand the anatomy & physiology of liver & biliary tree
- To be able to read & interpret the basics of liver function tests
- To be able to recognize the variable presentations of acute & chronic liver disease

- 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

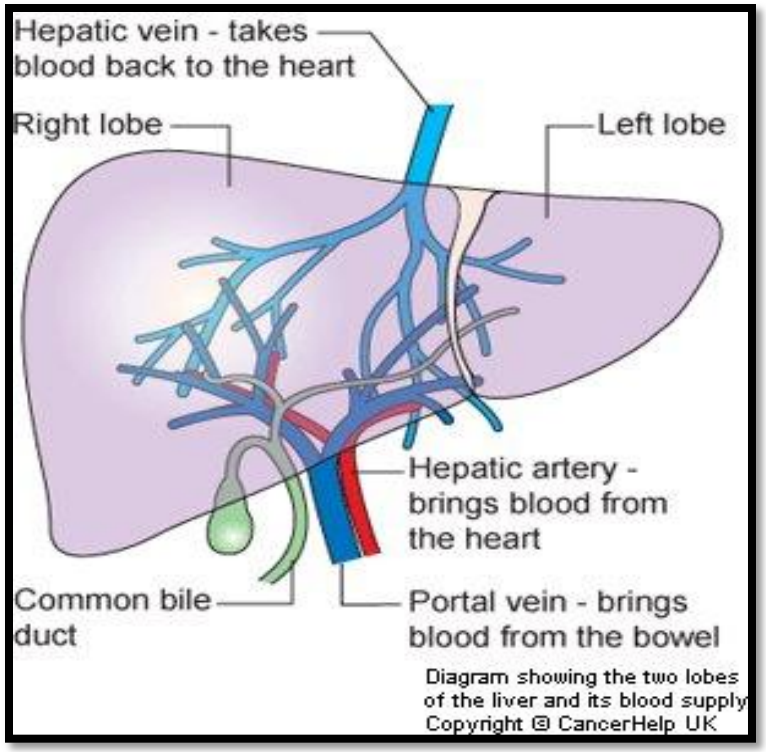
NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

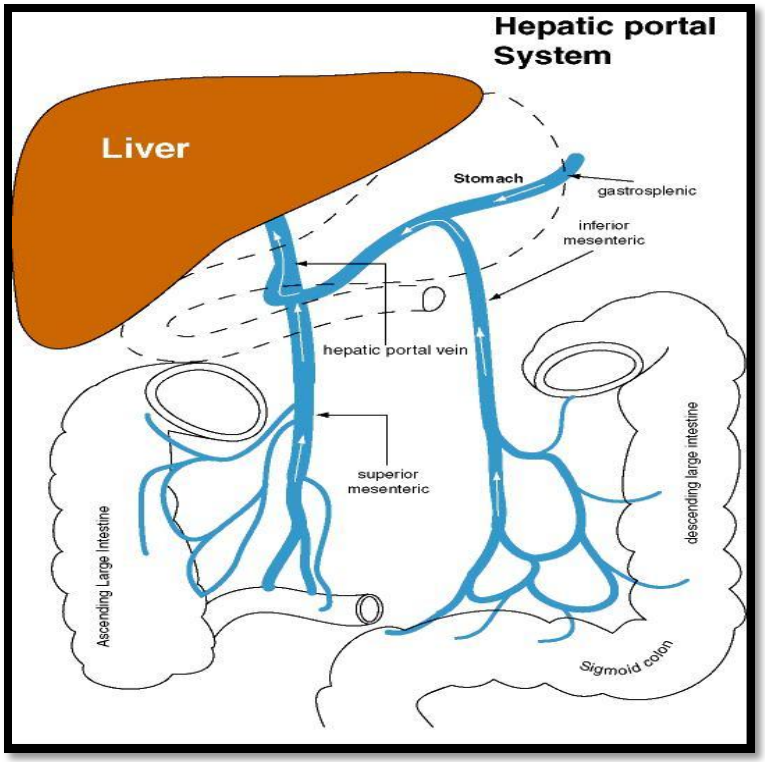
Liver anatomy



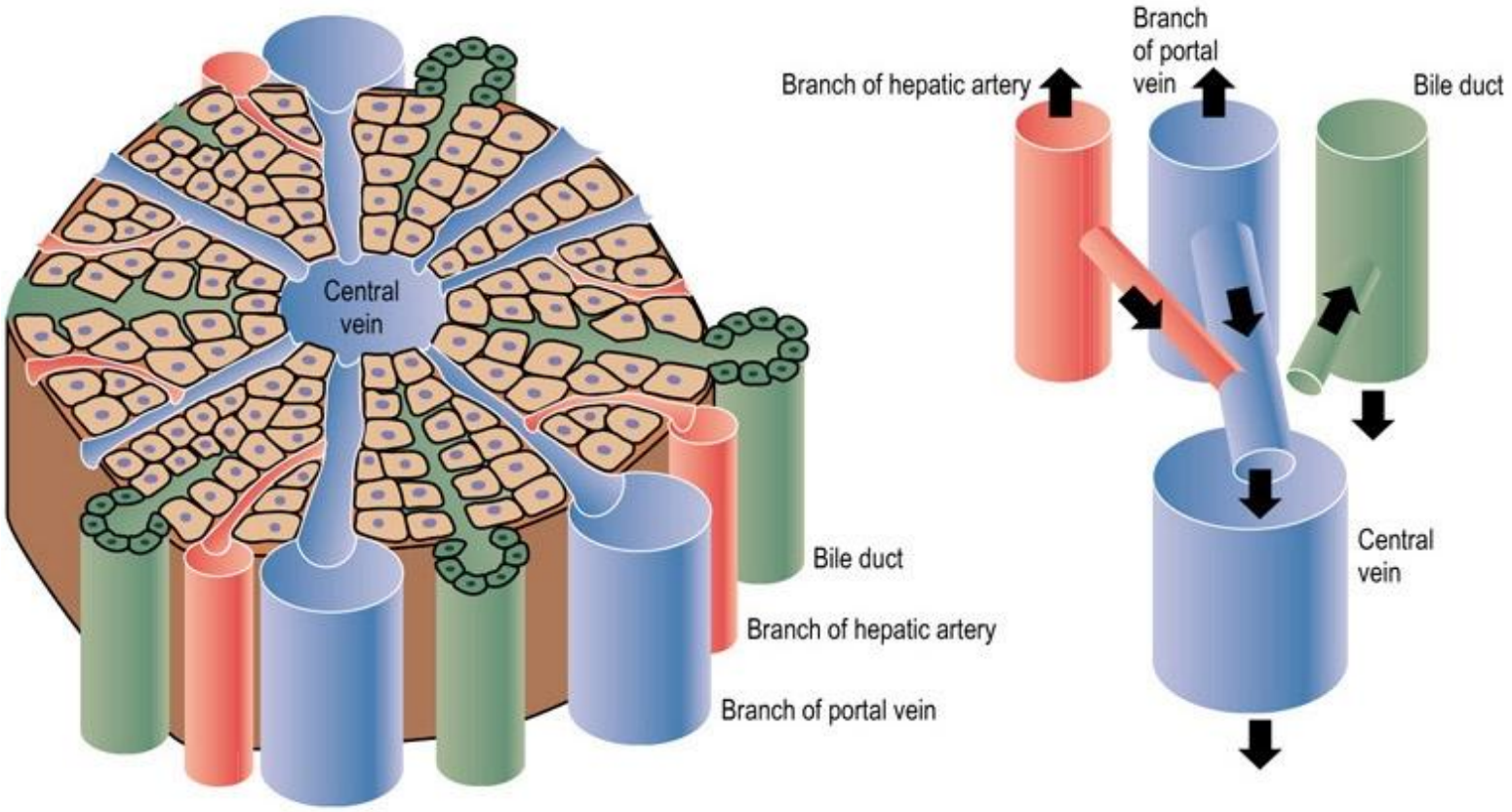
Liver blood supply

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

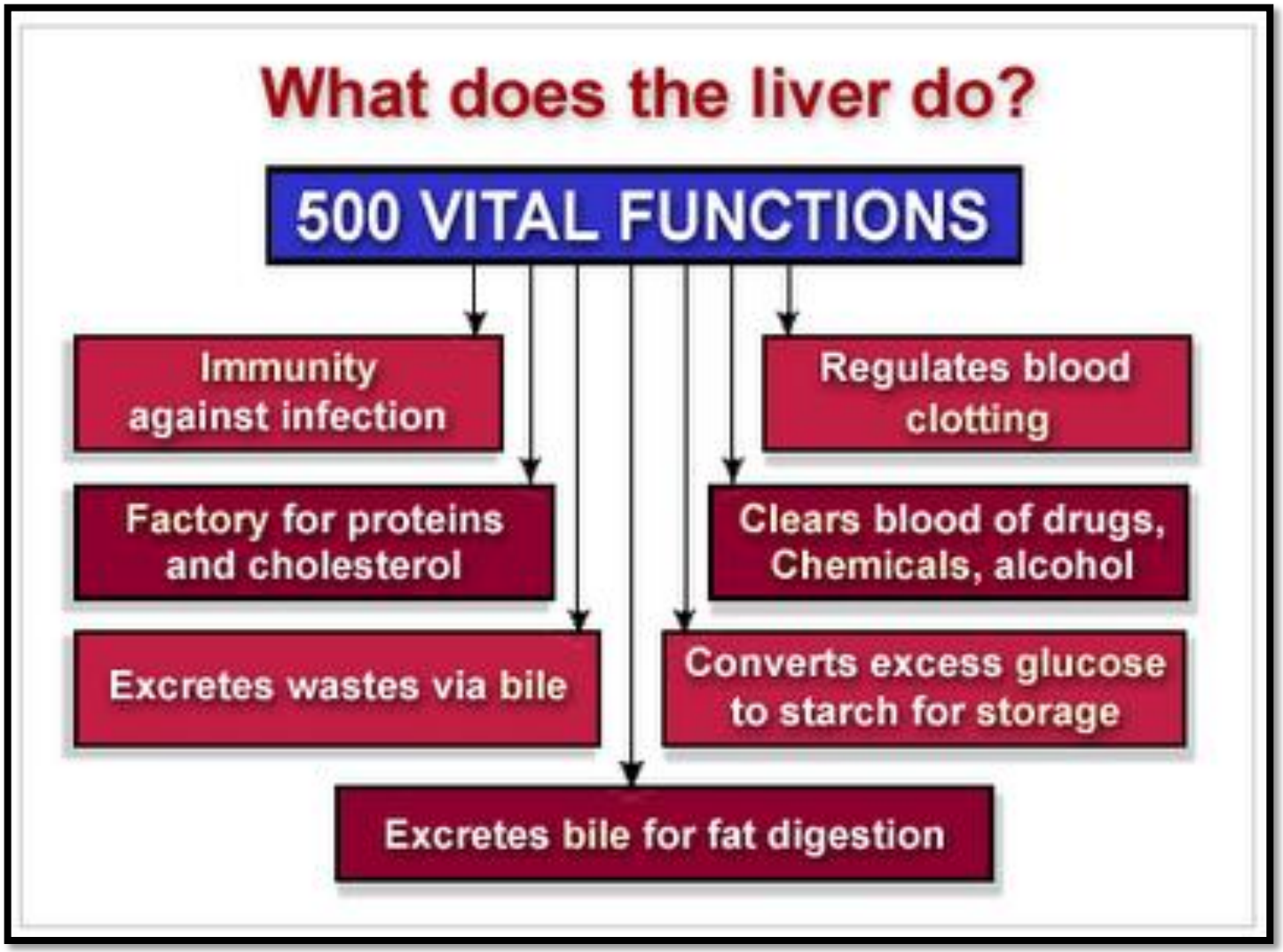




Liver Histology



Liver functions



Liver FUNCTION tests

Synthetic Function

1- Glucose

2- Plasma proteins (albumin, globulins, Clotting factors)

3-Lipids: cholesterol, triglycerides 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 B_{12}

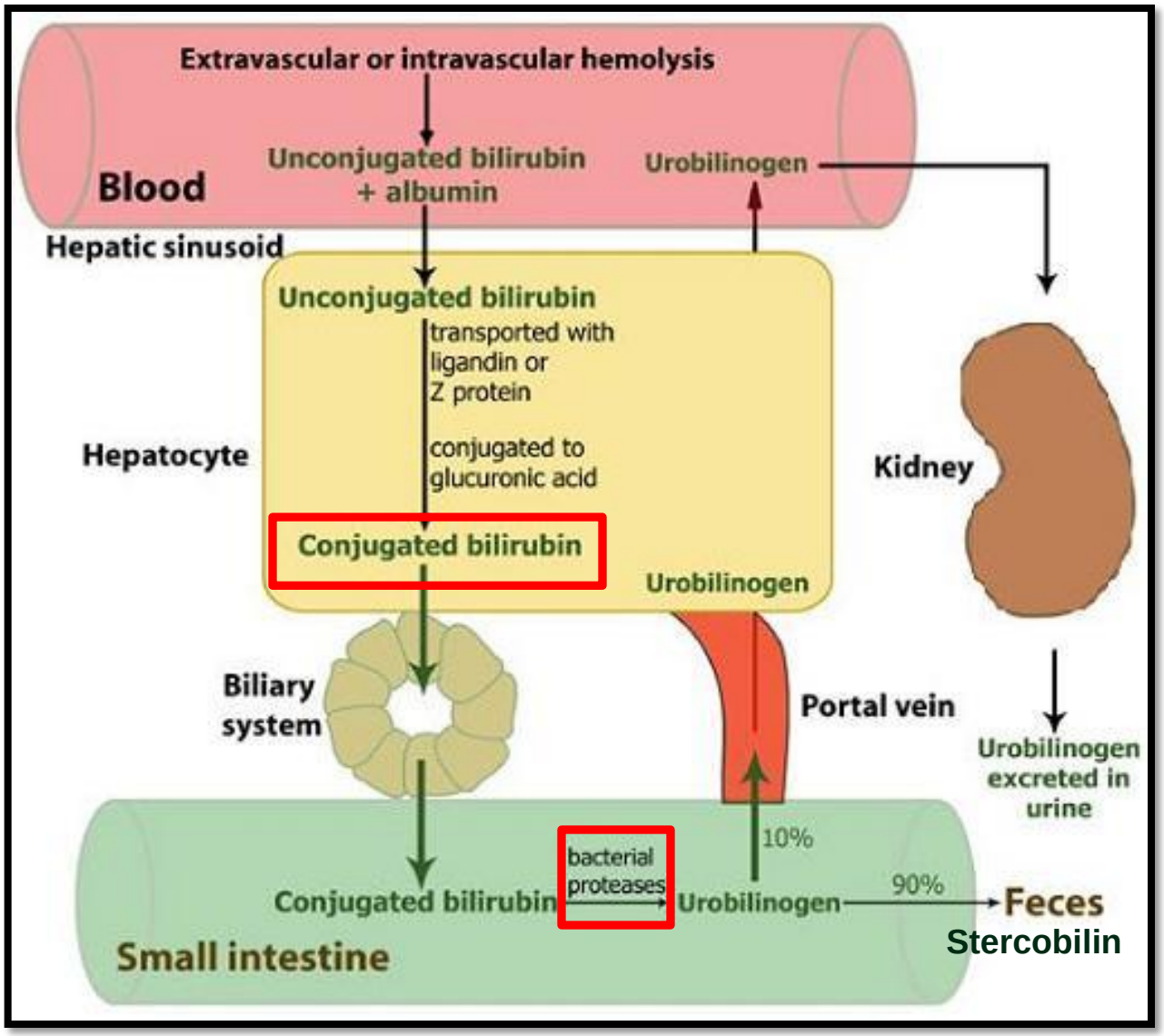
What are the liver function markers?

Liver enzymes # LFTs

- **Enzymatic markers:**
  - ALT
  - AST
  - ALP
  - GGT

- **Synthetic function markers:**
  - Glucose
  - Bilirubin (indirect/direct)
  - Bile acids
  - Albumin, Globulins
  - Clotting factors (PT &PTT)
  - Urea (formed from NH3 & AAs)

Bilirubin metabolism



Hyperbilirubinemia: important rules

- The term jaundice, derived from the French word (jaune), meaning (yellow)
- Hyperbilirubinemia (HB)= 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.

Hyperbilirubinemia

- Conjugated/Direct HB ⇔ Liver disease

- Unconjugated/Indirect HB is mostly non-liver related (RBC destruction)
- EXCEPT ?

Causes of un-conjugated HB

Haemolysis ;

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

Non- haemolysis;

1- Breast feeding/Milk Jaundice

2- Criglar Najjar syndrome

3- hypothyroidism

4- Gilbert syndrome,

5-Pyloric stenosis

Patterns for liver diseases:

A) Hyperbilirubenemia <u>with</u> elevated liver enzymes (more common)

B) Hyperbilirubinemia <u>without</u> elevated liver enzymes

Patterns for liver diseases:

A) Hyperbilirubenemia with elevated liver enzymes:

1*) Cholestatic or obstructive* bile duct injury

GGT /ALP > AST/ALT **(+ Hyberbilli)**

2) *Hepatocellular or liver cell inj*ury:

ALT/AST > GGT/ALP **(+ Hyberbilli)**

3) Mixed: Mostly

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

Hyperbilirubinemia

- **B): Hyperbilirubinemia without elevated liver enzymes**
  - **Unconjugated HB**:
    - Criggler Najjar syndrome
    - Glibert disease
  - **Conjugated HB:**
    - Dubin Johnson syndrome
    - Rotor disease

Un-conjugated hyperbilirubinemia **with normal LFTs**

- **Criggler Najjar syndrome:**
  - reduction in **glucouronyl transferase enzyme** (type 2) or OR totally absence (type 1)…
  - Differences??

- **Gilbert syndrome:**
  - older children & adults, observed when sick or dehydrated
  - Different mutation in the above mentioned enzyme.
  - not need treatment

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 intraheptaic 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

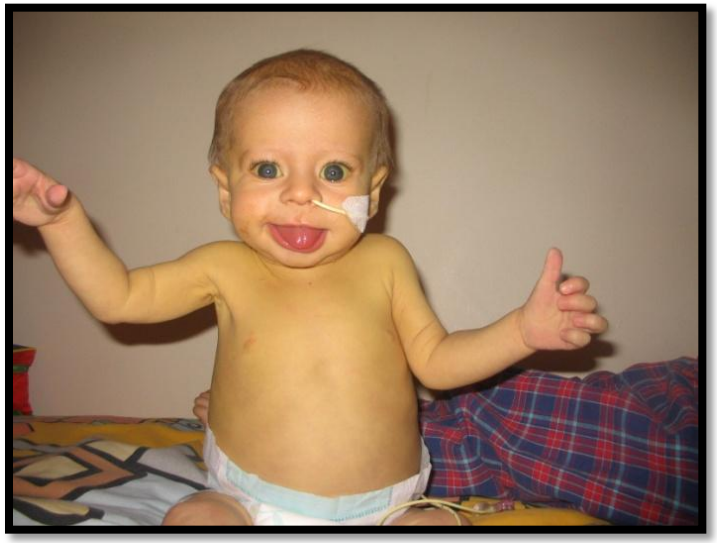
- **Cholestasis → chole= bile Stasis=stagnation**
- The obstruction of bile flow either:
  - **Mechanical block** (biliary atresia, stones…) or
  - **Functional block** (receptor & transporter levels):eg: progressive familial intrahepatic cholestasis (PFIC)

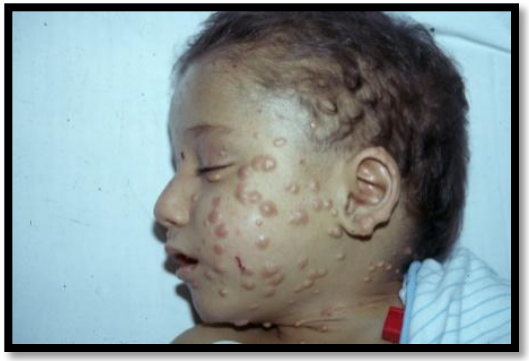
- **Cholestasis is characterized by an accumulation of compounds that cannot be excreted through the bile**
  - Conjugated/direct bilirubin→ jaundice (Cholestasis # jaundice)
  - Enzymes (ALT/AST>GGT/ALP)→ high liver enzymes in serum
  - Bile salts→ itchiness
  - Cholestrol→ xanthomas

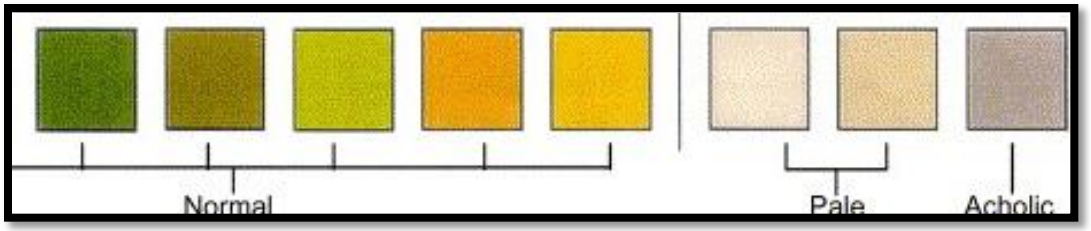
Presentation of cholestasis

- **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 cholestrol 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

- **STEP1: 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)

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

- 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

- Idiopathic neonatal hepatitis and mimickers
  - —Cystic fibrosis
  - —Alpha 1-antitrypsin deficiency
  - —Hypopituitarism/hypothyroidism
  - —Neonatal iron storage disease

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**

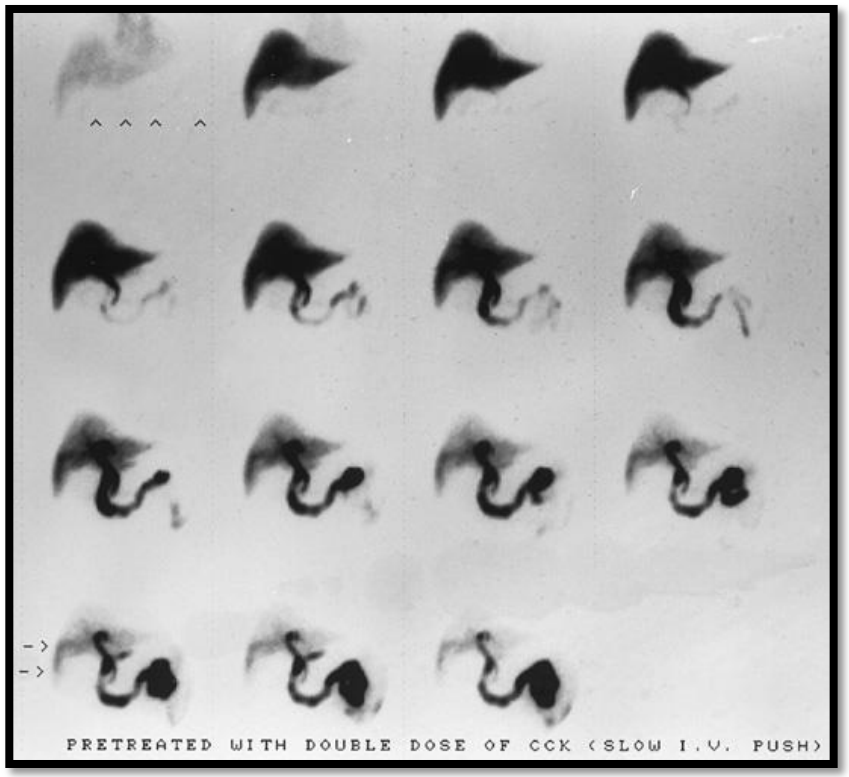
BA - Diagnosis

- **Clinical presentation**:
  - It presents with **signs of cholestasis** (jaundice, acholic stool, pruritis, FTT) in the **first 2-6 weeks of life (MCQ)**

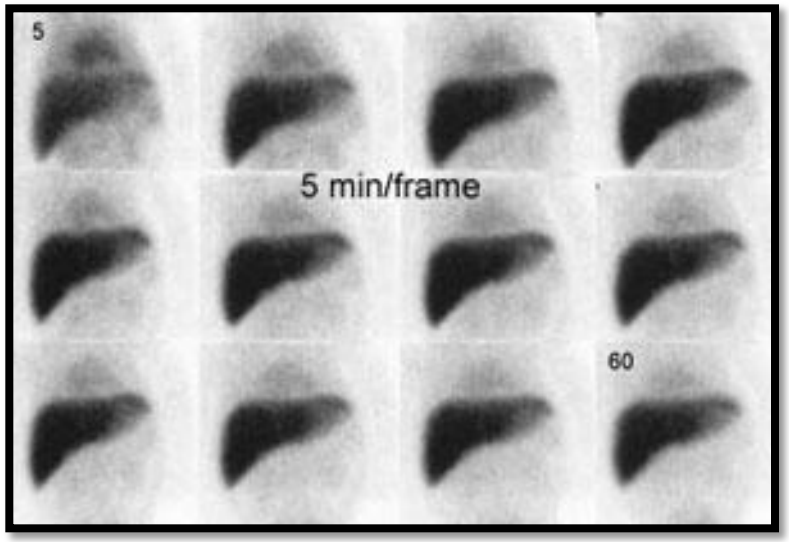
- **Abdominal US:** rule out other causes of biliary obstruction (choledochal cyst, GB stones…)

- **Hepato-biliary scintography = 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



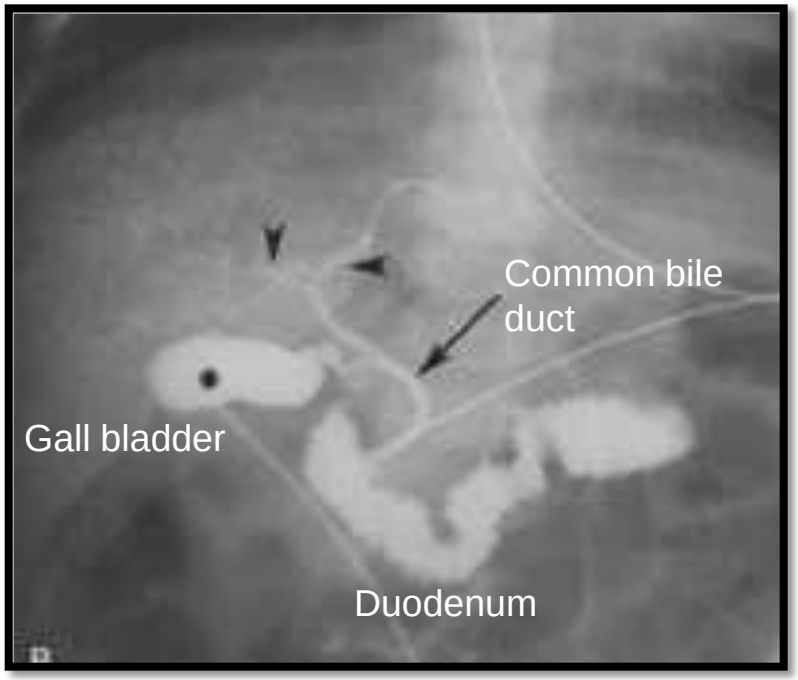
HIDA scan in BA patient

BA - Diagnosis

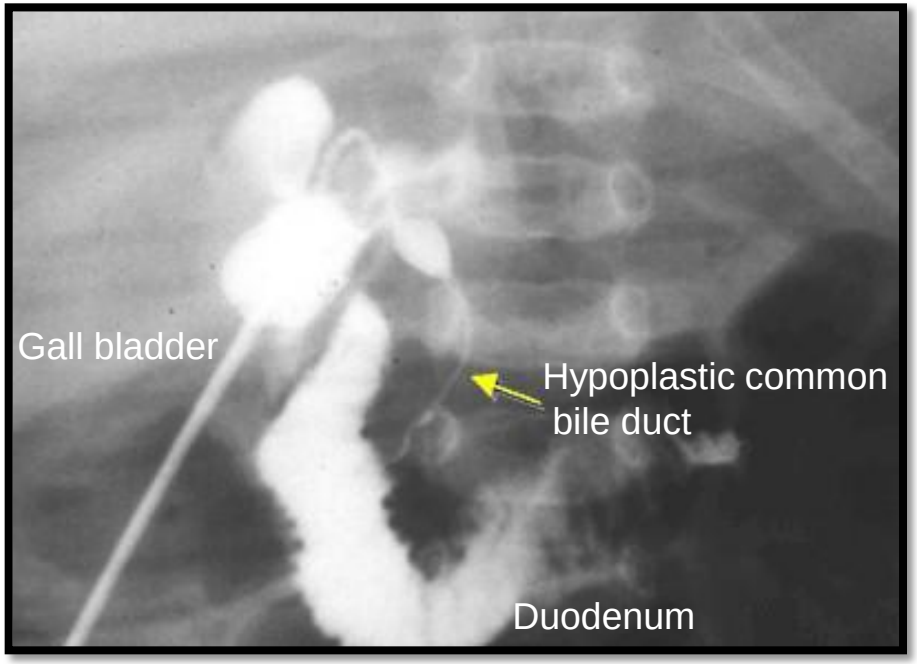
- **A liver biopsy:**
  - confirms the diagnosis by revealing characteristic findings (proliferation of the interlobular bile ducts, periportal fibrosis, and bile plugs in canaliculi and ductules)

- *Definitive diagnosis* is confirmed by **Intra-operative cholangiogram**

Definitive diagnosis is confirmed by Intra-operative cholangiogram



Normal study



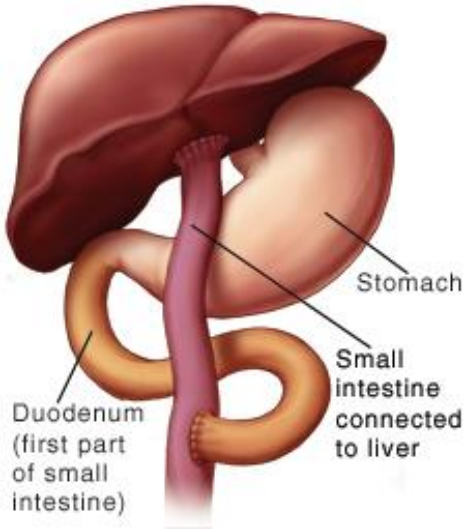
Abnormal study
(hypoplastic common bile duct)

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)

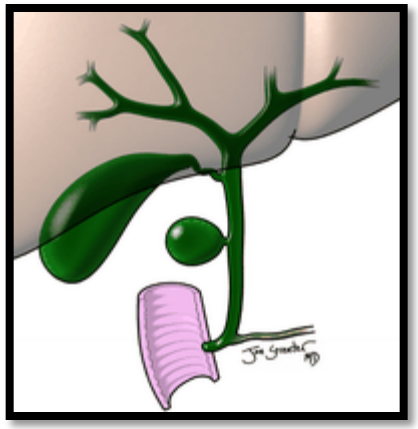
- **Liver transplantation** if:
  - Kasai failed, or
  - if late presentation (> 3 months) or
  - picture of decompensated liver disease

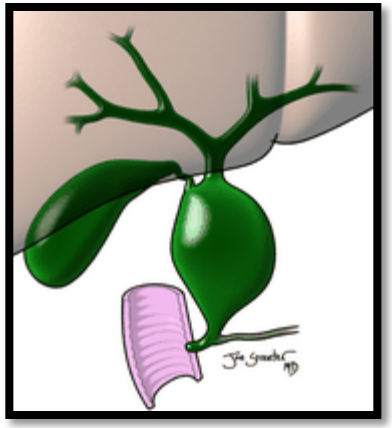


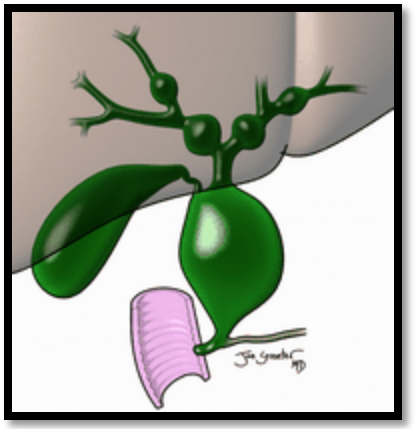
Choledocal cyst

- 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** (such as elastase, trypsin) that protect lung from neutrophil elastase destruction

- **A-1 AT deficiency cause:**
  - Neonatal liver disease
  - Adult emphysema lung disease (lung dis. is rare in children)

- **AR disease** (rare in our community)

- Abnormal mutation (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)

- **Treatment: supportive**

- **Prognosis:** varies (improve over time ….> chronic liver disease

Neonatal Hepatitis

- “Idiopathic" neonatal hepatitis = **an <u>aetiology has not been identified</u>**

- 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

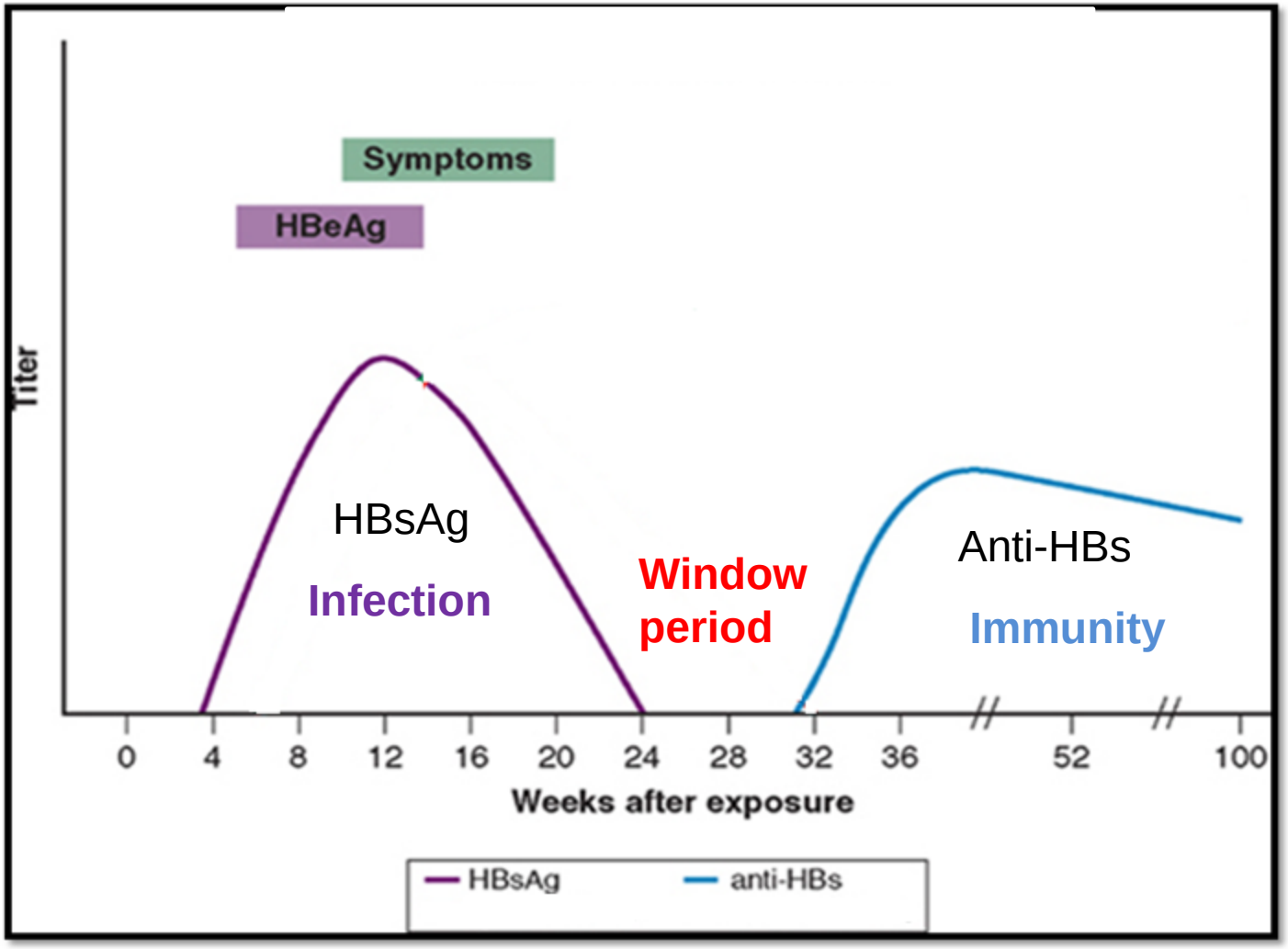
HEPATITIS A

- **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)

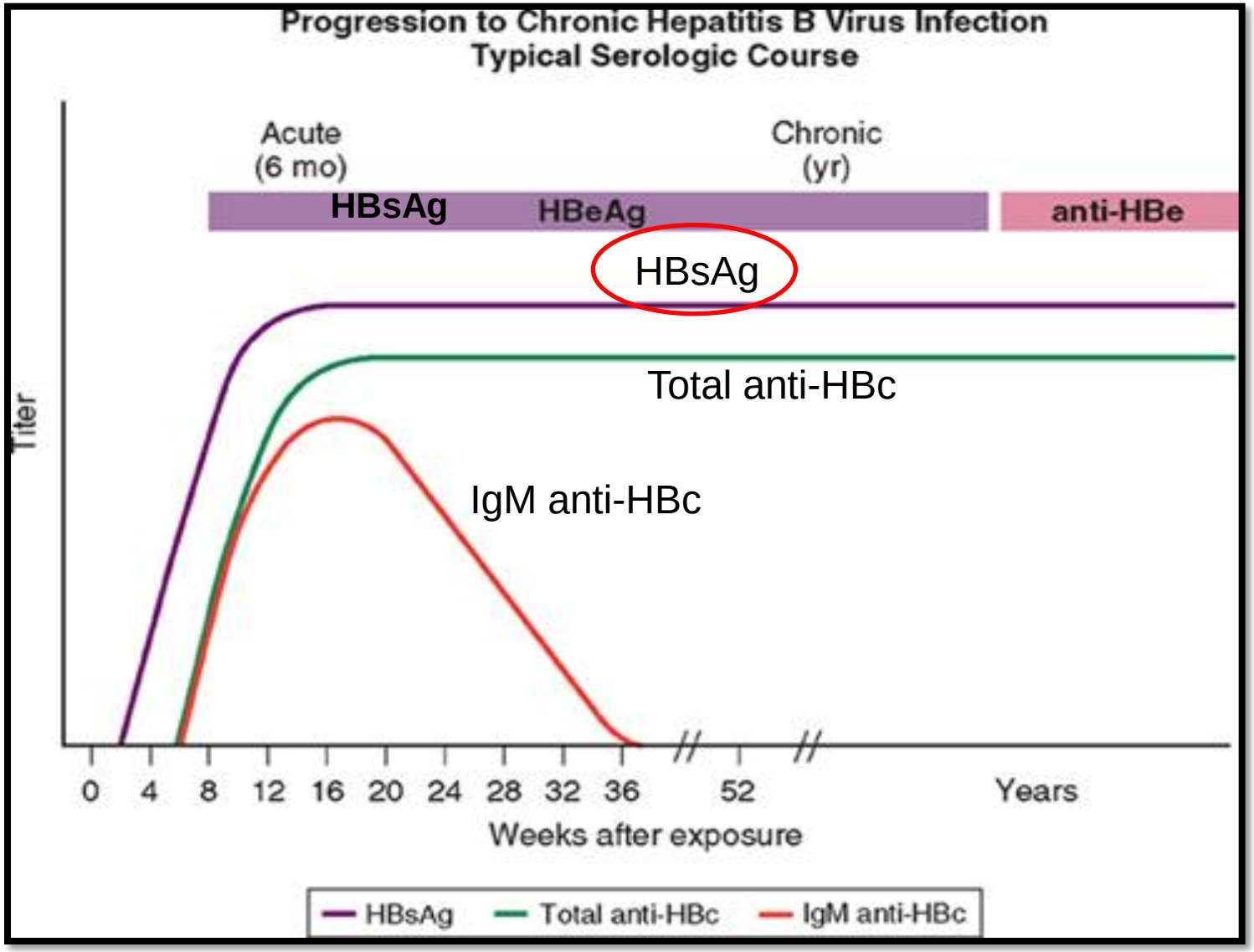
Hepatitis B

- 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**

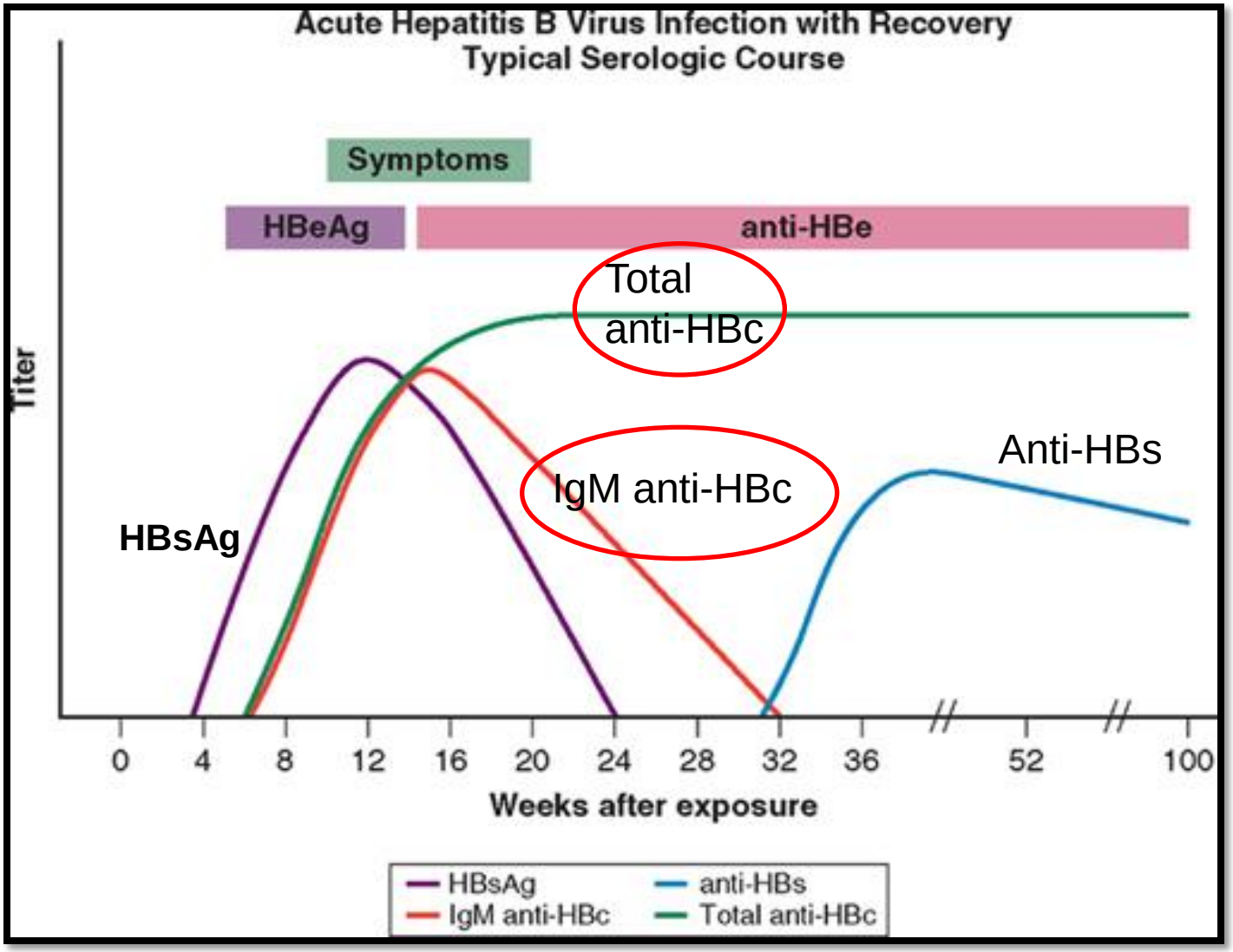
HBV serology markers



Chronic hepatitis



HBV serology markers.. recovery



Hepatitis B serological markers

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive 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

Treatment

- **Newborn of Hep BsAg-positive mothers (MCQ):**
  - **Hep. B Immunoglobulins** (within 12 hrs of birth)
  - **Hep. B Vaccine after birth** (within 7 days after birth, then at 1 month & 6 months)

- Older children: antiviral meds
  - ??? Wait & observe (spontaneous recovery, new better antiviral meds)

Hepatitis C

- Hepatitis C virus (HCV) causes acute hepatitis, which **progresses to chronic disease (End-stage liver disease can occur in up to 10 %)**
- Fulminant hepatitis rarely has been described
- Risk of transmission similar to hepatitis B
- **Diagnosis** is based on the detection of
  - persistently elevated anti-HCV antibodies and
  - **confirmed** by PCR for HCV RNA

Hepatitis C

- **Treatment**: (15-65%) antiviral Rx (new generation, > 95% effective)
- Spontaneous viral clearance from acute infections can occur in pediatrics (15-56%)
- **Prophylaxis**: no vaccine yet

Hepatitis D

- Hepatitis D virus (HDV) infection occurs only in patients who have HBV infection

- 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

- Associated primarily with intravenous drug abuse

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

?? Questions PART 4

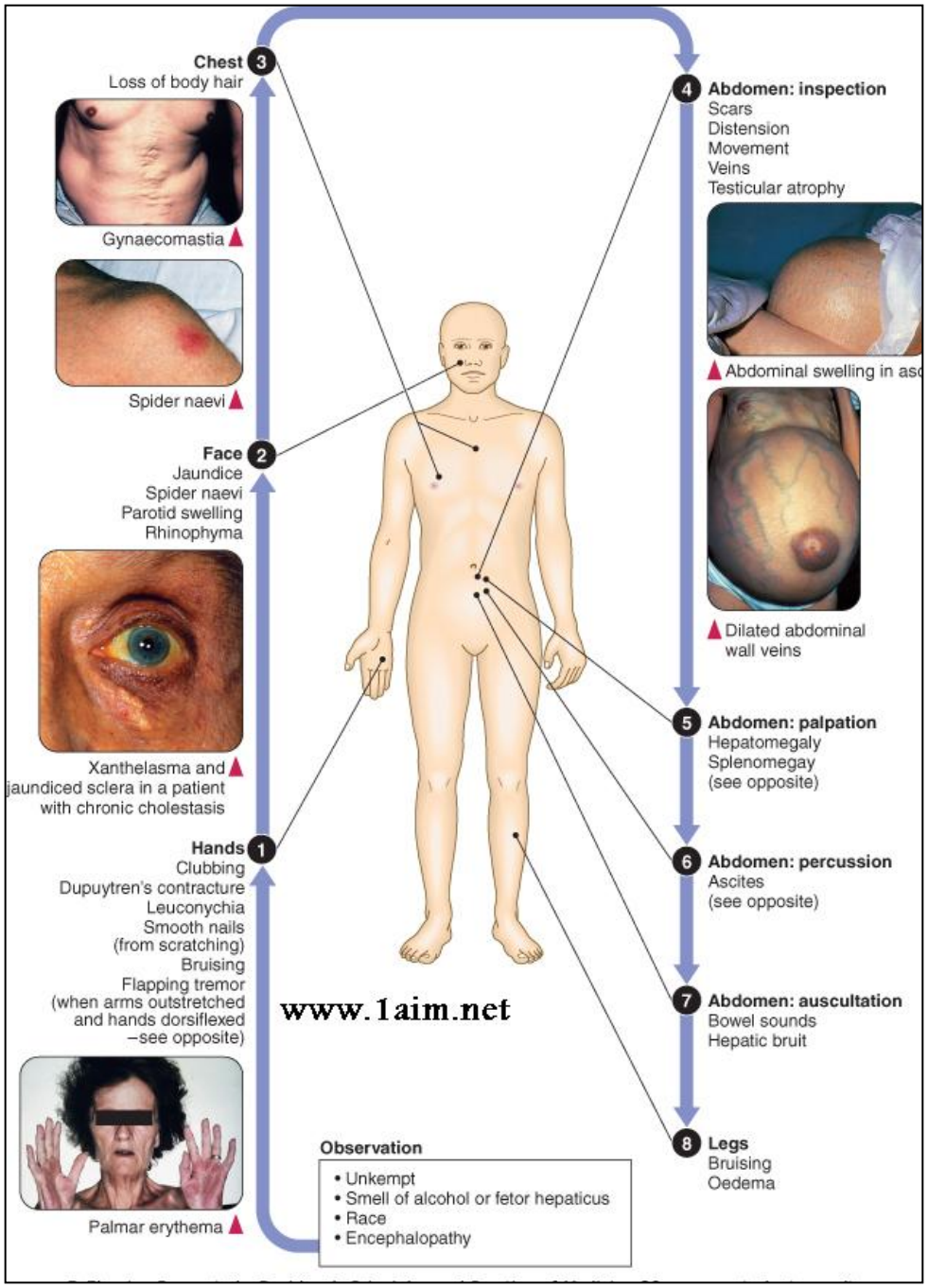
Chronic hepatitis

- **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; exposure to hepatotoxic drugs; or metabolic, or systemic disorders

- Can progress to CLD if the primary disease not treated well

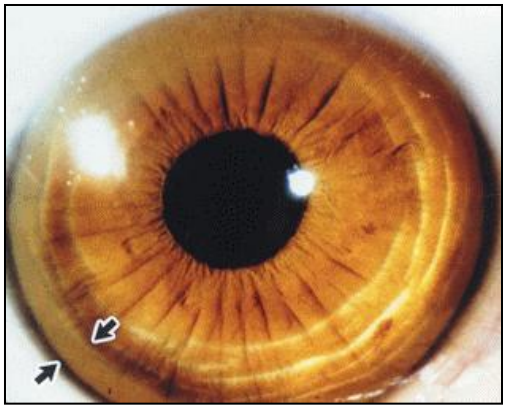
Signs of CLD


Chest 3
Loss of body hair
Gynaecomastia
Spider naevi
Face 2
Jaundice
Spider naevi
Parotid swelling
Rhinophyma
Xanthelasma and jaundiced sclera in a patient with chronic cholestasis
Hands 1
Clubbing
Dupuytren's contracture
Leuconychia
Smooth nails (from scratching)
Bruising
Flapping tremor (when arms outstretched and hands dorsiflexed –see opposite)
Palmar erythema
4 Abdomen: inspection
Scars
Distension
Movement
Veins
Testicular atrophy
Abdominal swelling in asc
Dilated abdominal wall veins
5 Abdomen: palpation
Hepatomegaly
Splenomegay
(see opposite)
6 Abdomen: percussion
Ascites
(see opposite)
7 Abdomen: auscultation
Bowel sounds
Hepatic bruit
8 Legs
Bruising
Oedema
Observation
• Unkempt
• Smell of alcohol or fetor hepaticus
• Race
• Encephalopathy
www.1aim.net

Wilson disease (a must to know)

- AR disorder
- caused by a defect in biliary copper **excretion**

- **Excessive copper accumulation in the:**
  - **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

- **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 **congestive heart failure, 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 tumers*)
- **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