Liver disease in children

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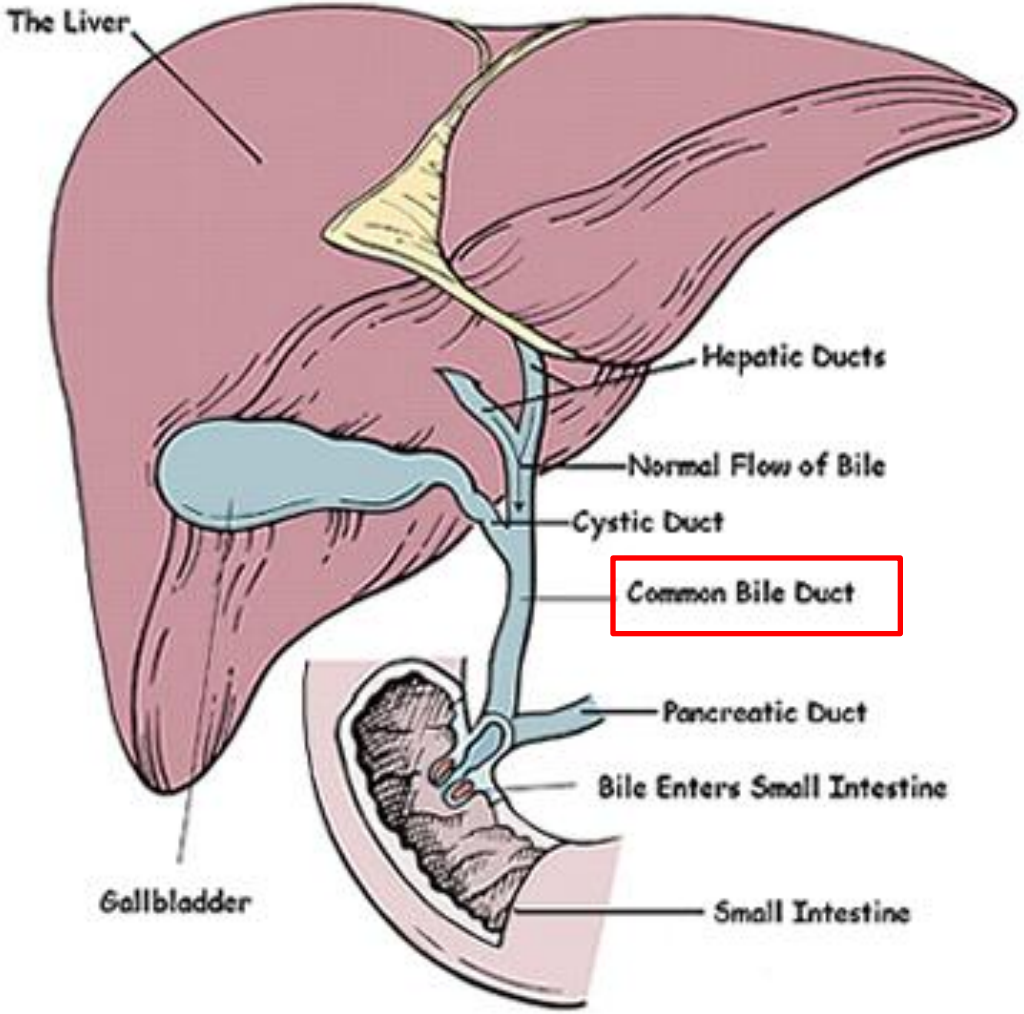
Objectives

- To understand the anatomy & basic physiology of liver & biliary tree
- To be able to read & interpret the basics of liver function tests
- 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 them appropriately

PART - 1

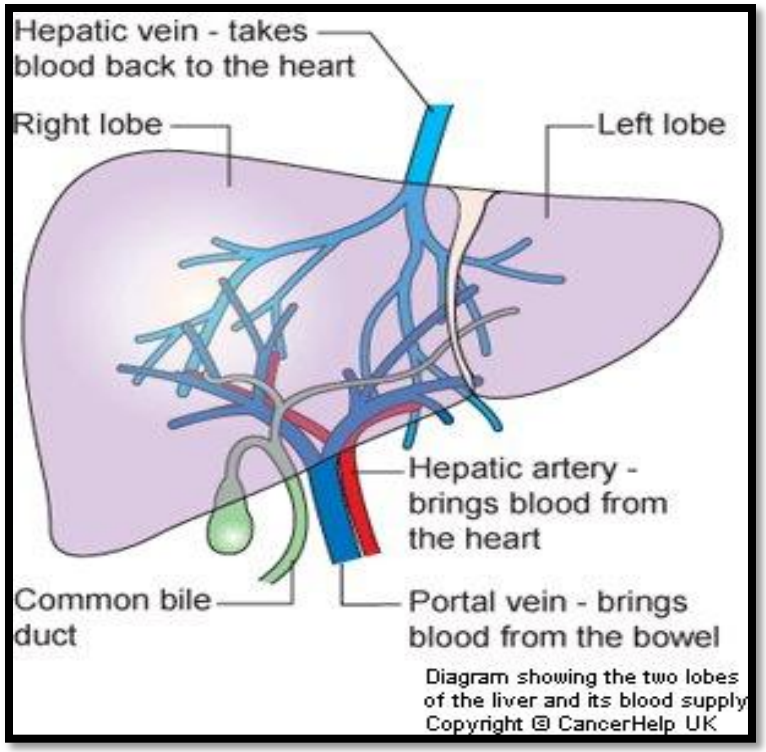
NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

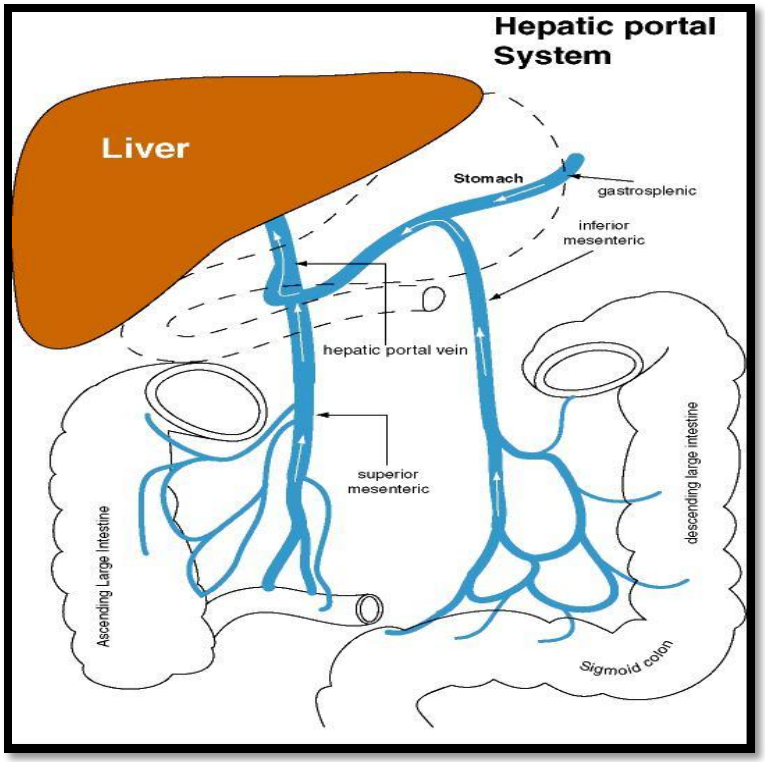
Liver anatomy



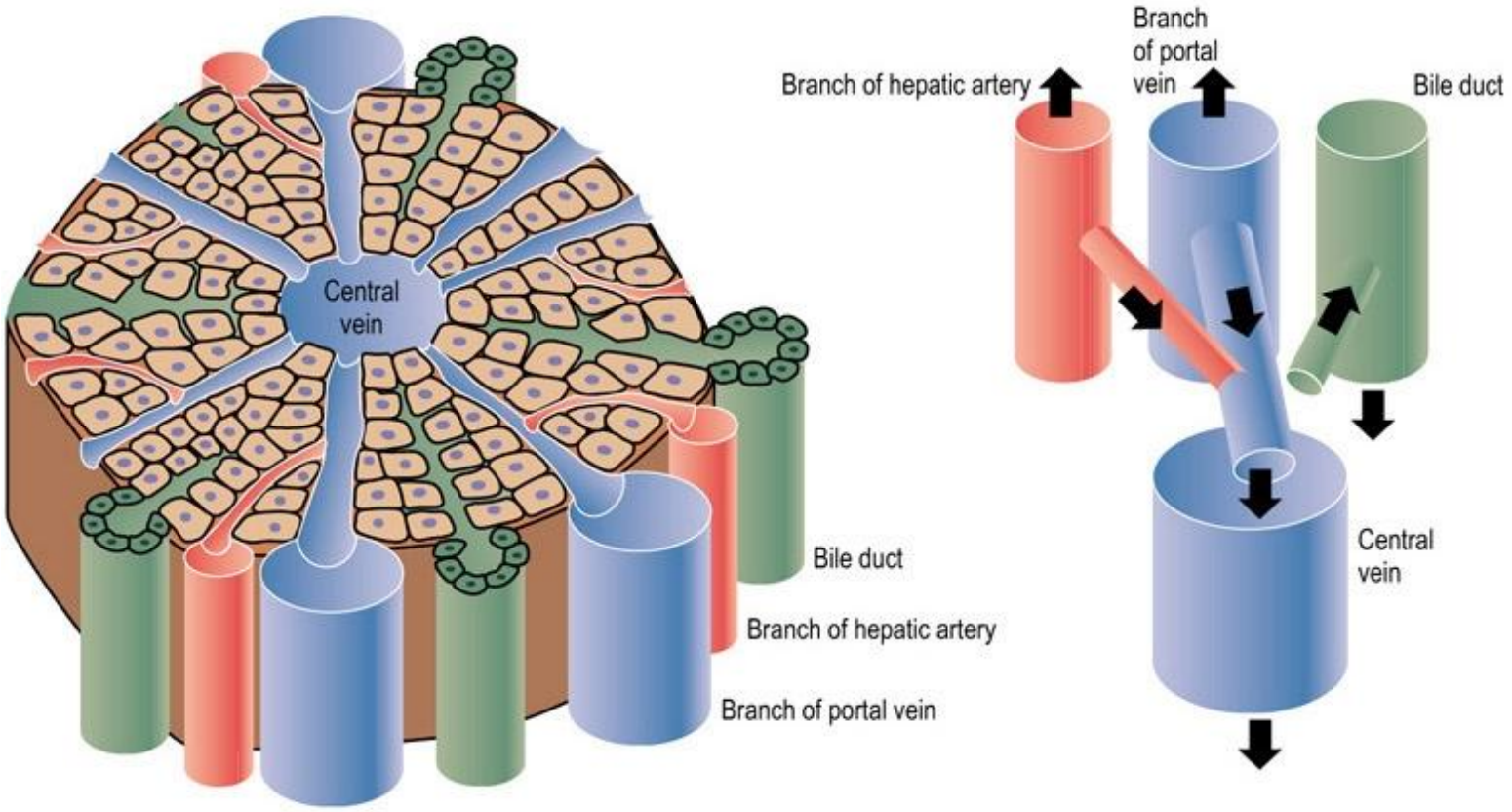
Liver blood supply

- Liver has **dual Blood supply** resources ;
  - 70% from portal vein
  - 30% from Hepatic artery





Liver Histology



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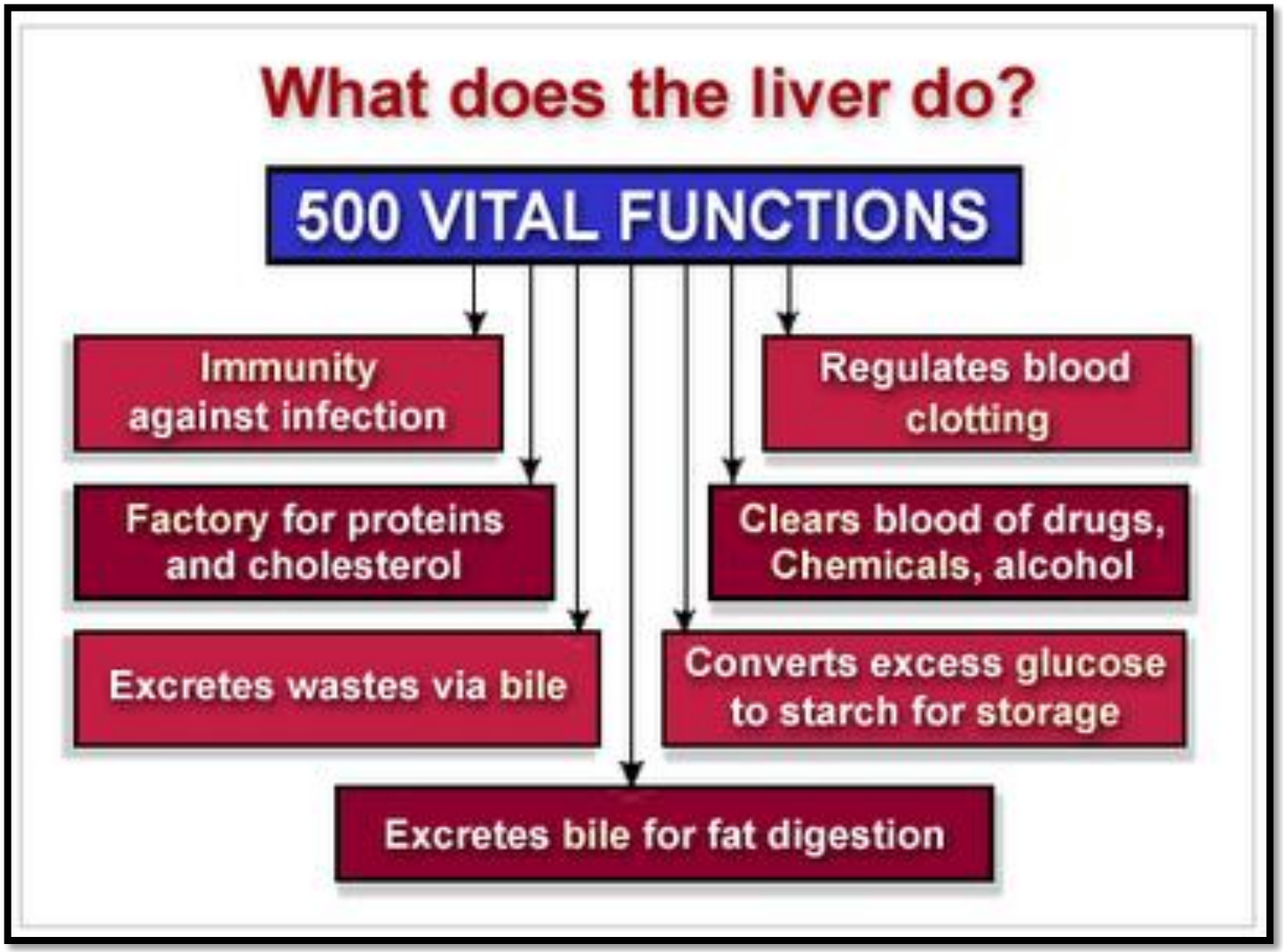
Liver functions



What are the liver function markers?

Liver enzymes # LFTs

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

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

- The laboratory findings of **liver injury** can be divided broadly into two patterns:

  1) Cholestatic or obstructive bile duct injury:

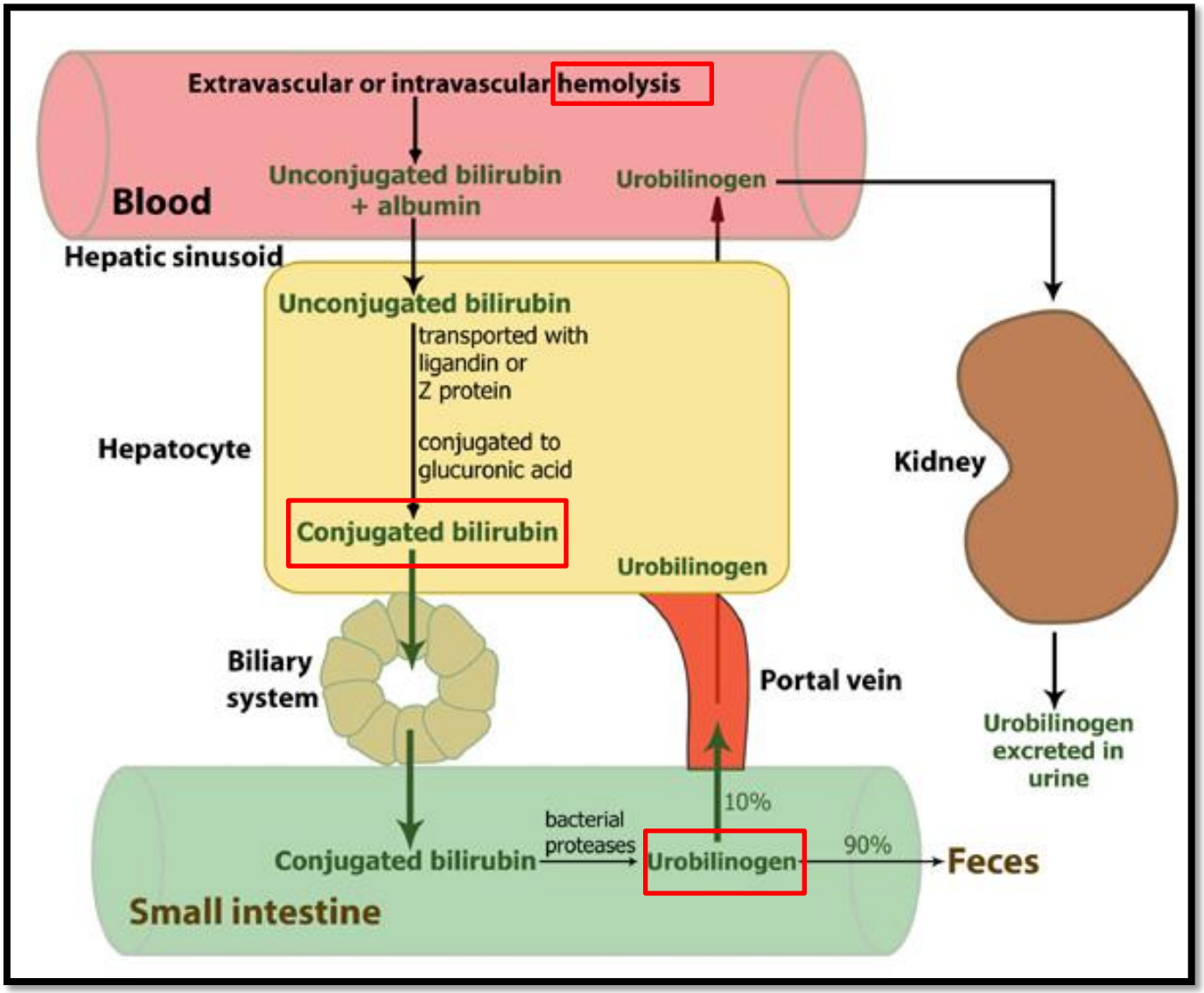
  GGT /ALP > AST/ALT

  2) Hepatocellular or liver cell injury:

  ALT/AST > GGT/ALP.

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

Bilirubin metabolism



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

  - **Older children = adults liver diseases:** Wilson disease, Auto-immune hepatitis, ect

- **The main presenting** symptoms of liver disease is **jaundice**

- **Any jaundice after 2 weeks of age is pathological & should be investigated (MCQ)**

Types of liver diseases

- **Liver disease can be:**

1- Primary cholestatic/obstructive or

2- Hepato-cellular dominant picture

3- MIXED PICTURE-Usually the case

Cholestatic liver disease

- **Cholestasis → chole= bile Stasis=stagnation**

  is the obstruction of bile flow (mechanical or functional block)

- Cholestasis # jaundice

- It is characterized by an accumulation of compounds that cannot be excreted through the bile
  - Conjugated bilirubin
  - Enzymes (ALT/AST>GGT/ALP)
  - Bile salts
  - Cholestrol)

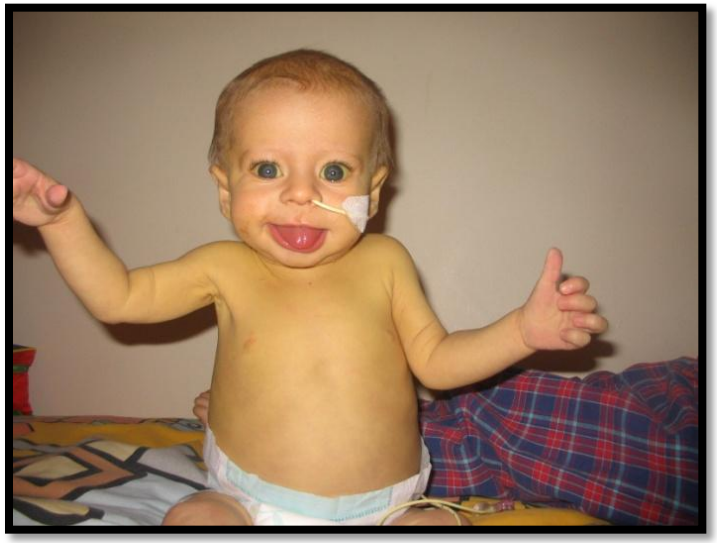
Presentation of cholestasis

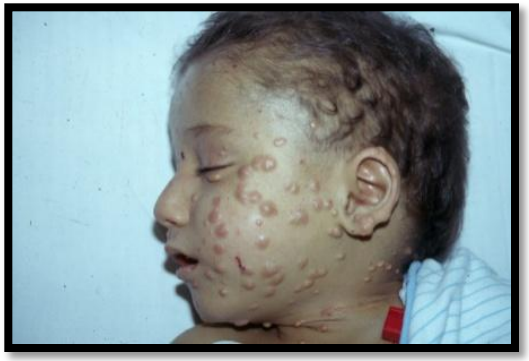
- **Jaundice** (accumulation of conjugated bilirubin)

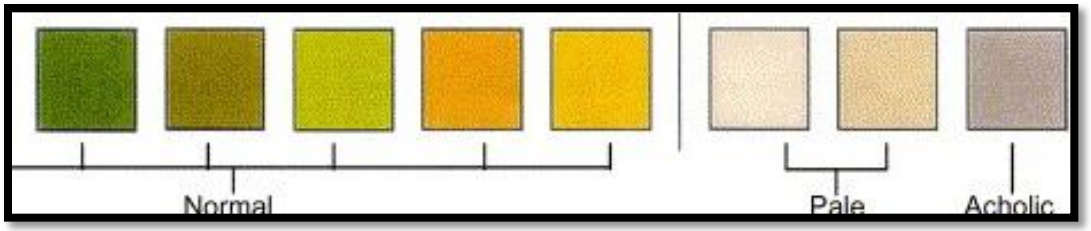
- **Pale stool (Acholic stool)… Why?? (MCQ)**
- **Dark and foamy urine** (bile salts in the urine)
- **Pruritis** (accumulation of bile salts under the skin)
- **Xanthomas depositions** (accumulation of cholestrol)
- Hepatomegaly +/- Splenomegaly (Portal HTN, Storage disease, infiltrative proceses)

- 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 & lab)

STEP 2: Rule out obstruction such as Biliary atresia, Choledocal cyst and GB stones (Abdm US, HIDA scan, Liver biopsy)

STEP 3: Investigate the treatable conditions:

- Infections(UTI, TORCH infections)
- Hypothyrodism, hypopituitarism
- Some metabolic disorders (Galactosemia, Tyrosenemia)

STEP 4: Further studies for other genetic causes

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

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 & CHILDREN

Biliary Atresia (BA)

- Biliary atresia is an obstruction 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 → infant death within 2 years If not treated

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

- The most frequent indication worldwide for liver transplantation among infants and children (not in KSA)

BA - Diagnosis

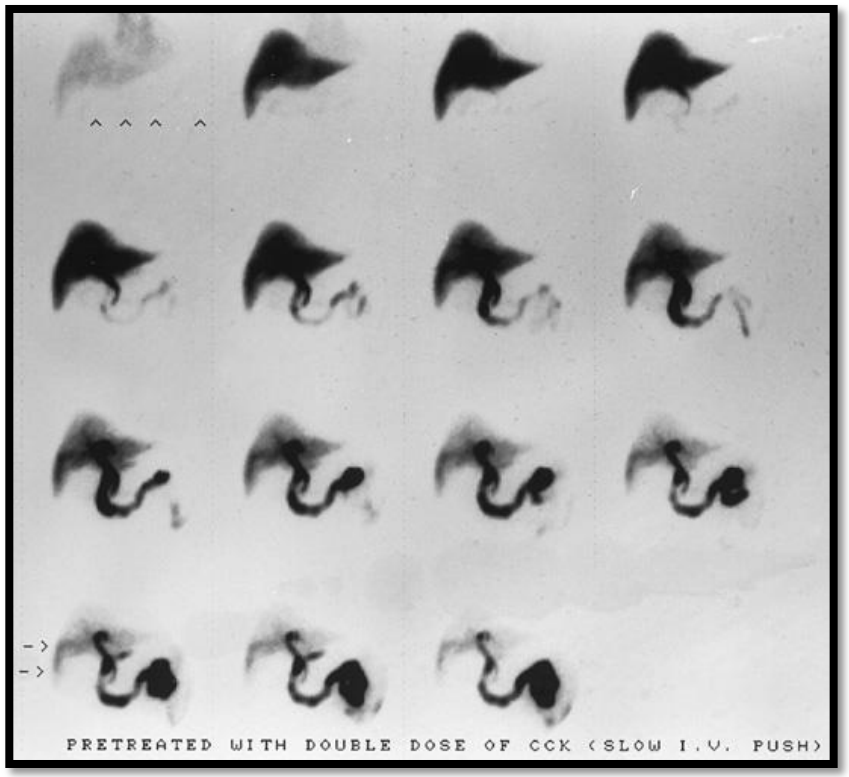
- **Abdominal US:** rule out other causes of biliary obstruction (choledochal cyst, GB stones…)

- **Hepato-biliary scintigraphy (HIDA scan):**

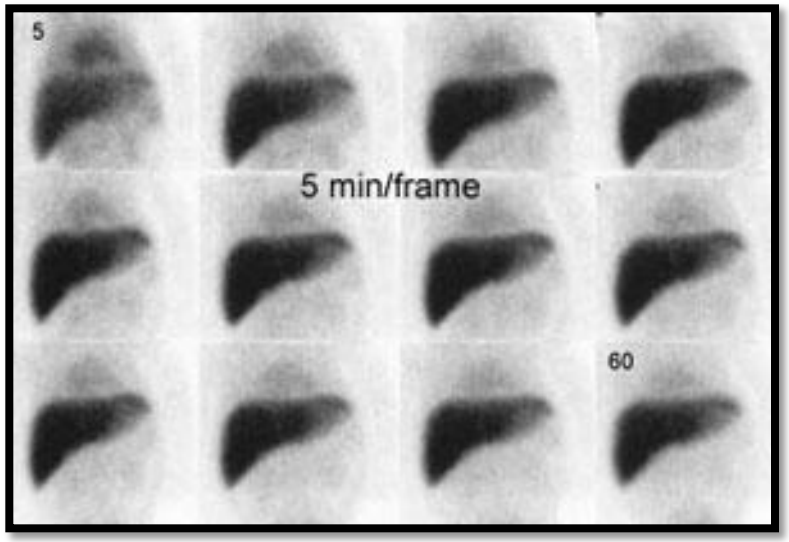
  shows good uptake of tracer and no excretion of it into the intestine, even 24 hours later (next slide)

- **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)

Hepato-biliary scintigraphy (HIDA scan)

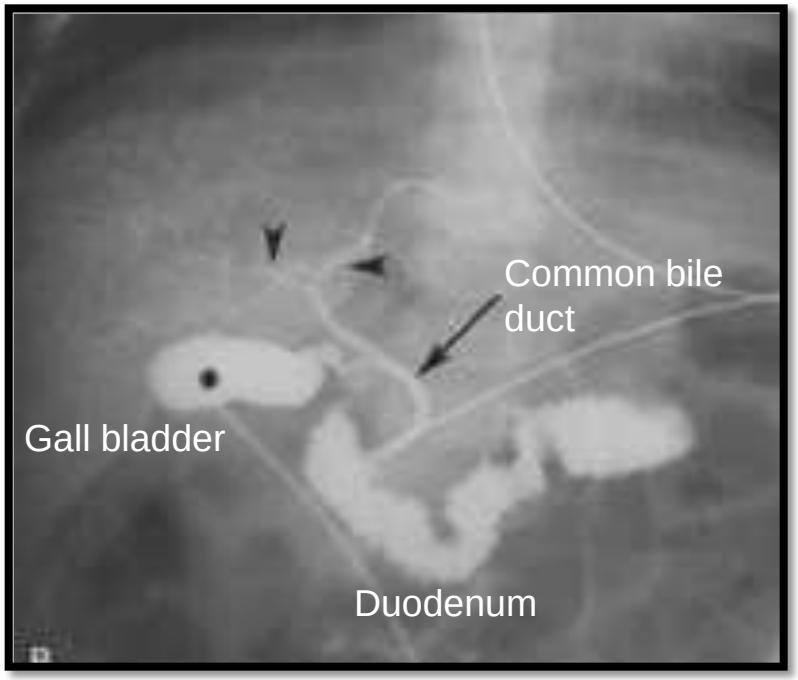


NORMAL HIDA SCAN

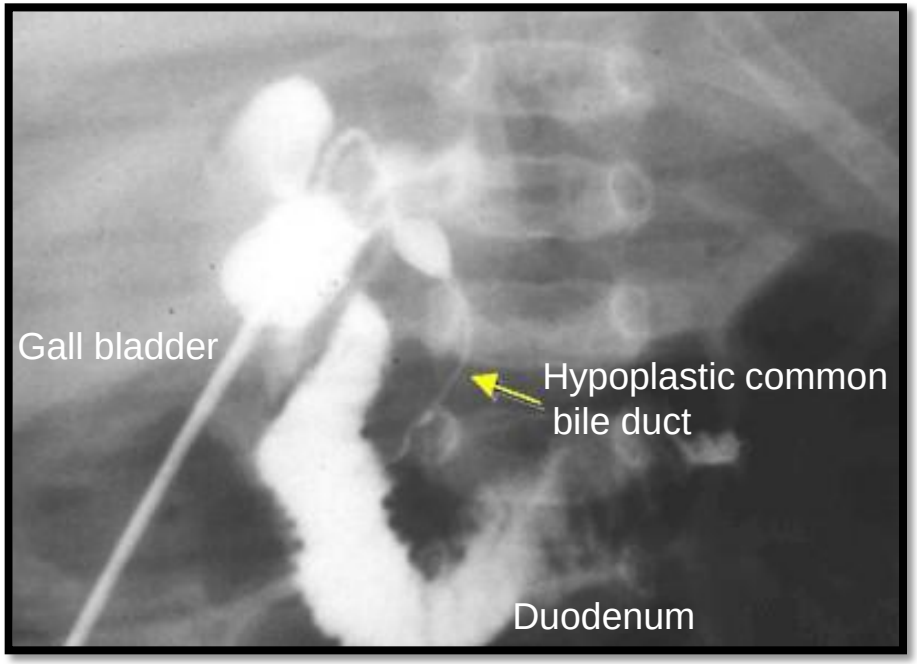


HIDA scan in BA patient

Definitive diagnosis is confirmed by Intra-operative cholangiogram



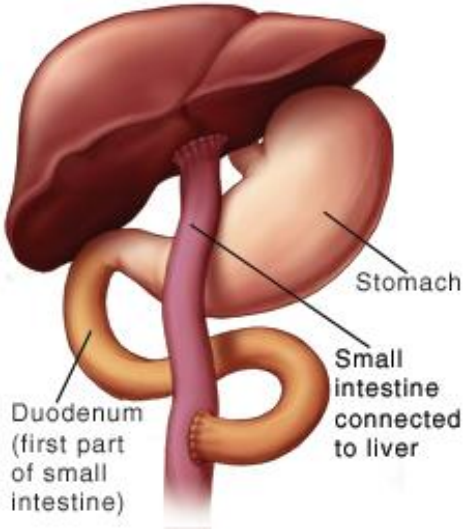
Normal study



Abnormal study
(hypoplastic common bile duct)

BA Management

- **Surgical correction (Kasai porto-entero-stomy) :**
- Should be done before 2 months of age (MCQ) (after this age, there is increased risk of fibrosis & subsequent cirrhosis)

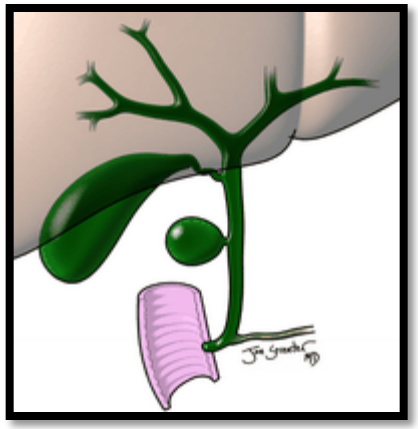


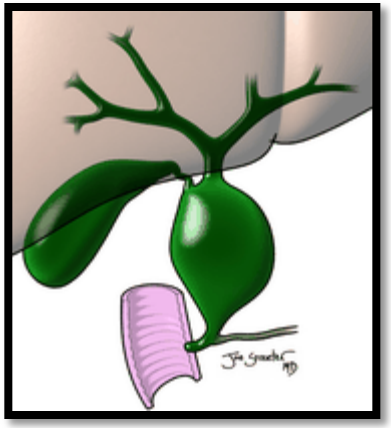
- **Liver transplantation** if Kasai failed, or if late presentation (> 3 months), or picture of decompensated liver disease

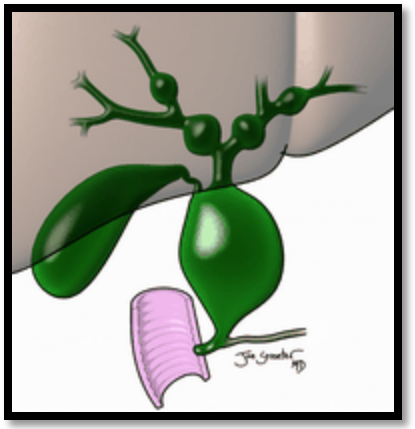
Choledocal cyst

- Cystic dilatation of the biliary tree at different levels → **obstructive picture**

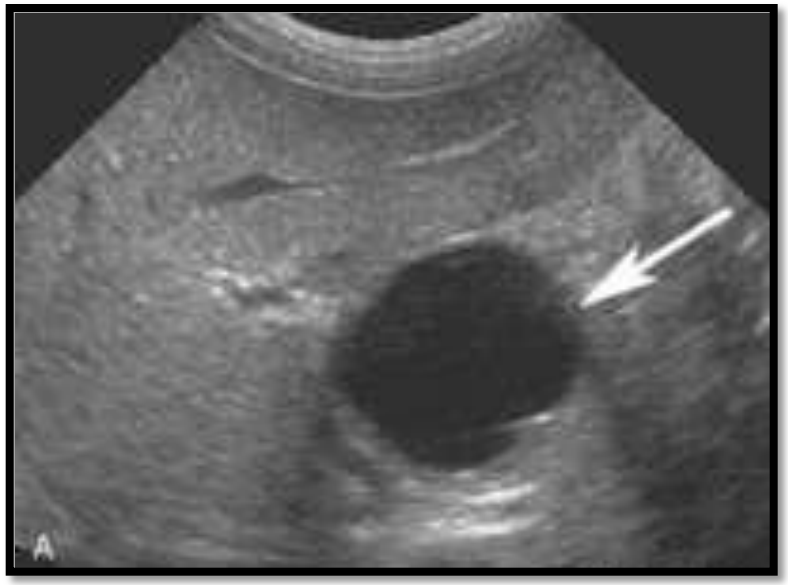
- Present with cholestasis picture, abdominal mass or asymptomatic, biliary stones or biliary carcinoma in adults







Choledocal cyst



Treatment: surgical excision

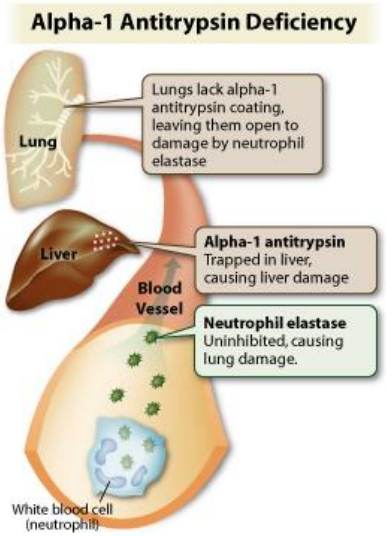
Alpha-1 Antitrypsin deficiency

- A-1 AT is a protease inhibitor (such as elastase, trypsin) that protect lung from neutrophil elastase destruction → its deficiency cause **neonatal liver disease** & **adult emphysema lung disease** (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

- **Dx: A-1 AT level & phenotyping (pi ZZ) & confirmed by Liver biopsy**

- **Treatment: supportive**
- Prognosis: varies (improve over time ….> CLD)



Neonatal Hepatitis

- “Idiopathic" neonatal hepatitis = an aetiology has not been identified

- The list get 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

Liver disease in older children = adults !!

- Infectious (Viral, Bacterial, Protozoal)
- Toxic (drugs, TPN)
- Ischemia (CR arrest, hypotention)
- Metabolic dis (CHO, FAT, Amino Acids, Metals)
- Autoimmune (AIH)
- 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, especially following ingestion of contaminated food

- Hepatitis A is often an-icteric (no jaundice) in young children (<5 y) and frequently is unrecognized.

HEPATITIS A

- The pathogen spreads primarily via the oral-fecal route (contaminated food)
- The disease typically is self-limited in children and often is clinically not clear

- No chronic carrier state is identified (fully recover or rarely death)
- Diagnosis of acute infection is based on the presence of anti-HAV IgM antibody in serum (MCQ)

- Treatment is supportive (IVF, Antipyretics)

Hep A prevention

- Hep. A vaccine:
  - 2 doses at 18 ms & 24 months

Hepatitis B

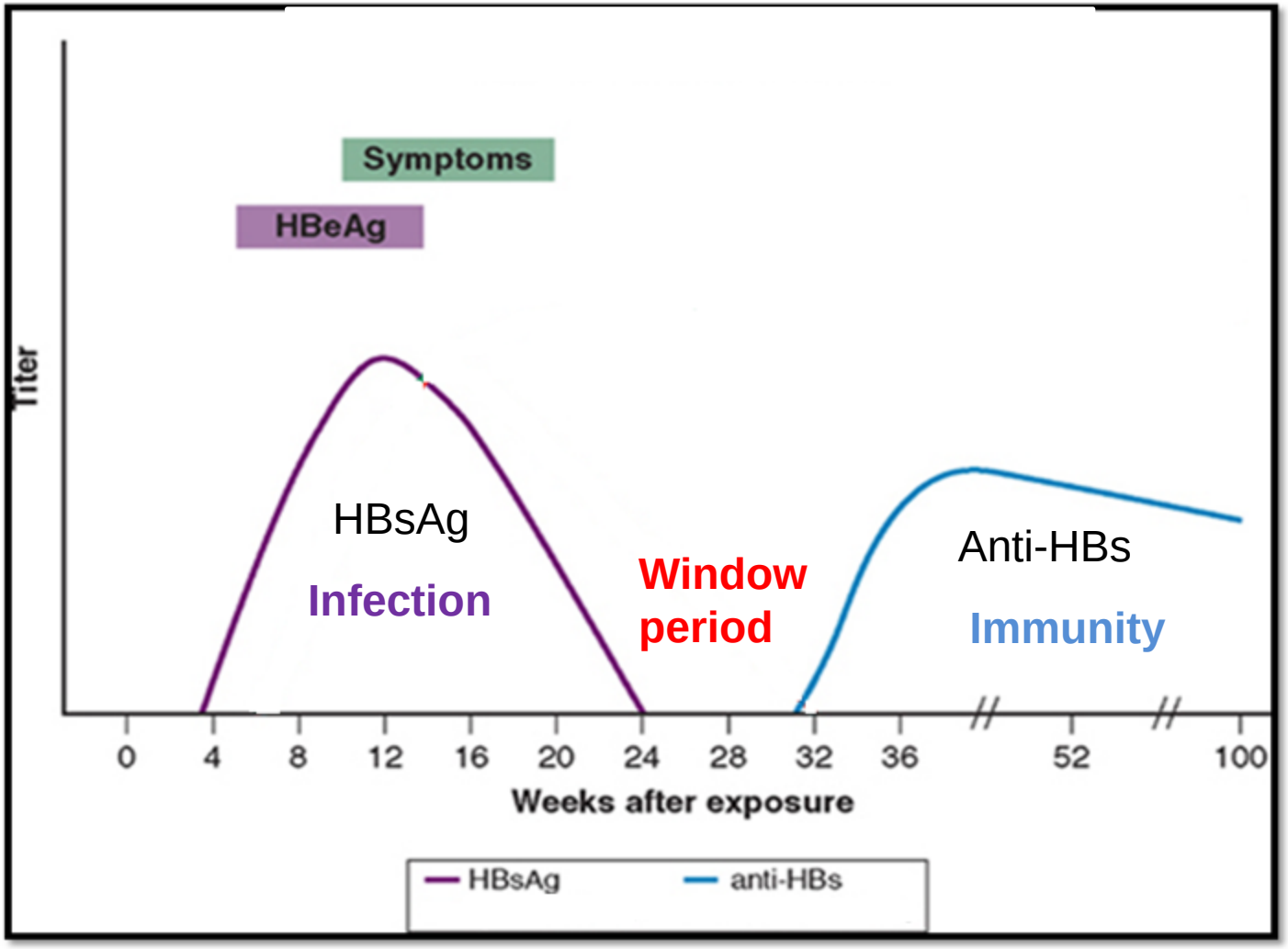
- Hepatitis B virus (HBV) infection can cause both acute and chronic hepatitis
- It can progress to cause **cirrhosis and hepatocellular carcinoma** if not treated (take long time to happen)

- Risk of transmission: primarily vertical (mother to baby) in children or via contaminated blood + other risk factors..

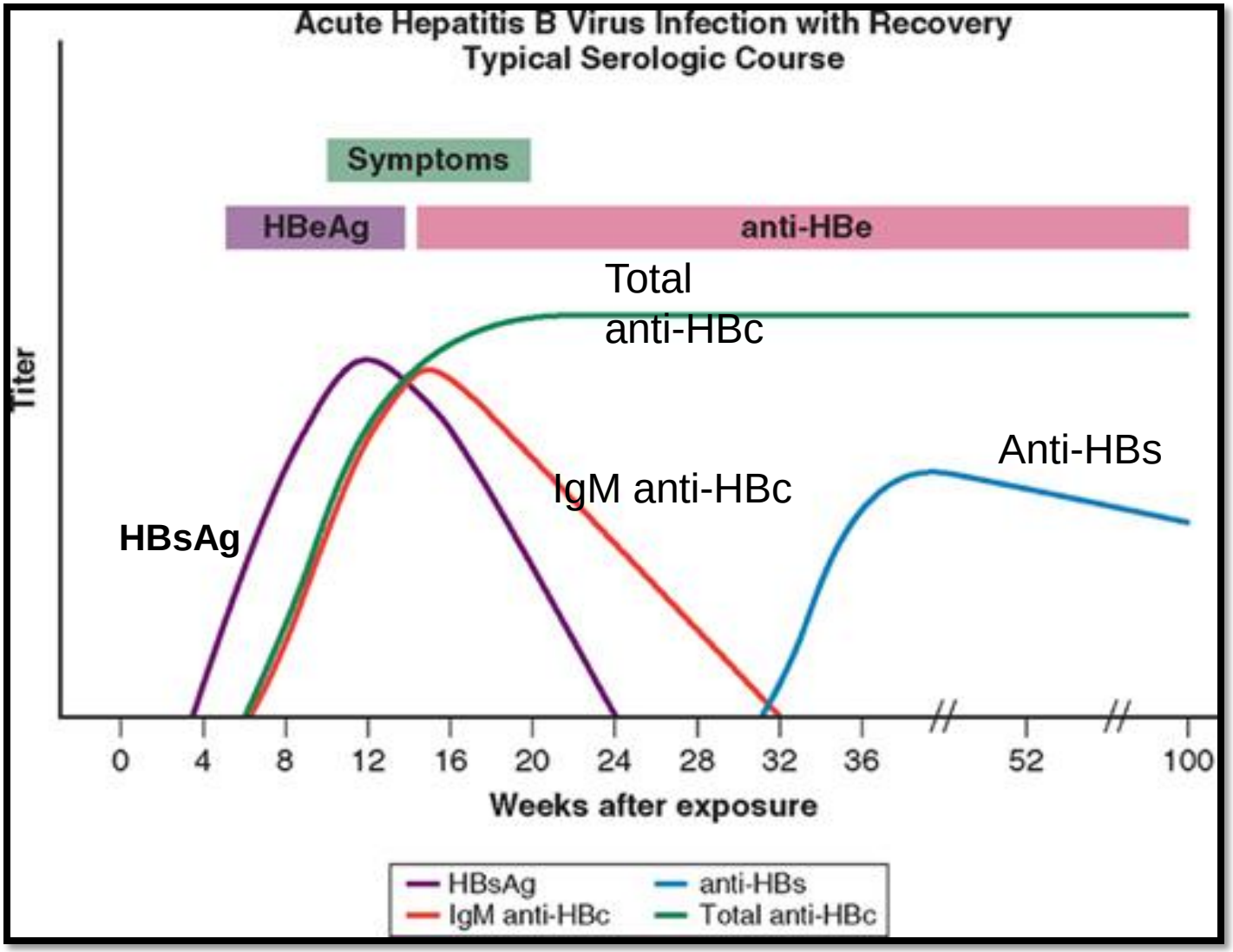
- **Diagnosis**: Hepatitis B surface antigen (HBsAg)

- **Chronic HBV infection** is associated with the persistence of HBsAg and HBV DNA for > 6 moths

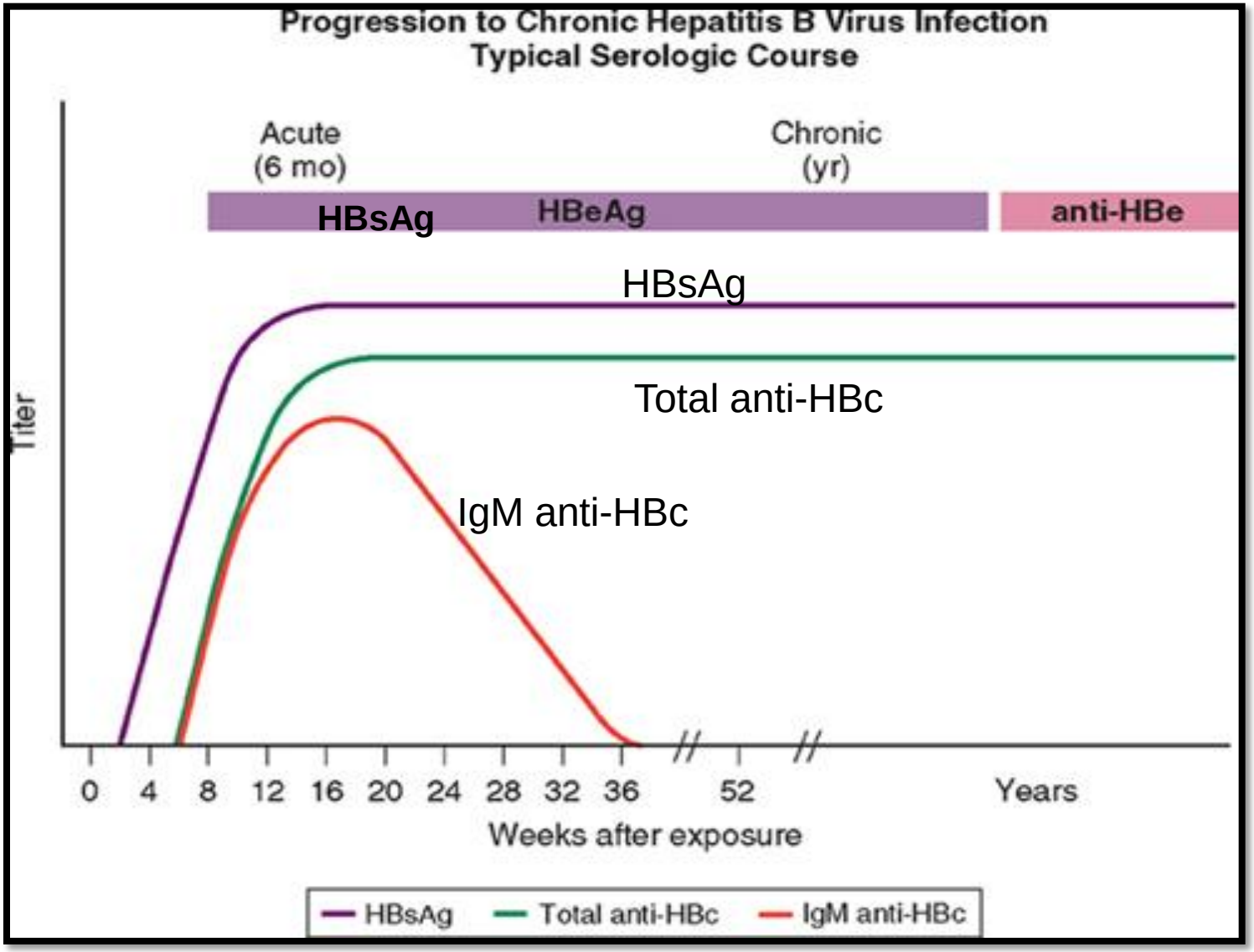
HBV serology markers



HBV serology markers.. recovery



Chronic hepatitis



Hepatitis B serological markers (for fun!!)

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 ??? 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 anti-HCV antibodies and confirmed by polymerase chain reaction (PCR) for HCV RNA
- Prophylaxis: no vaccine yet
- Treatment: antiviral Rx

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

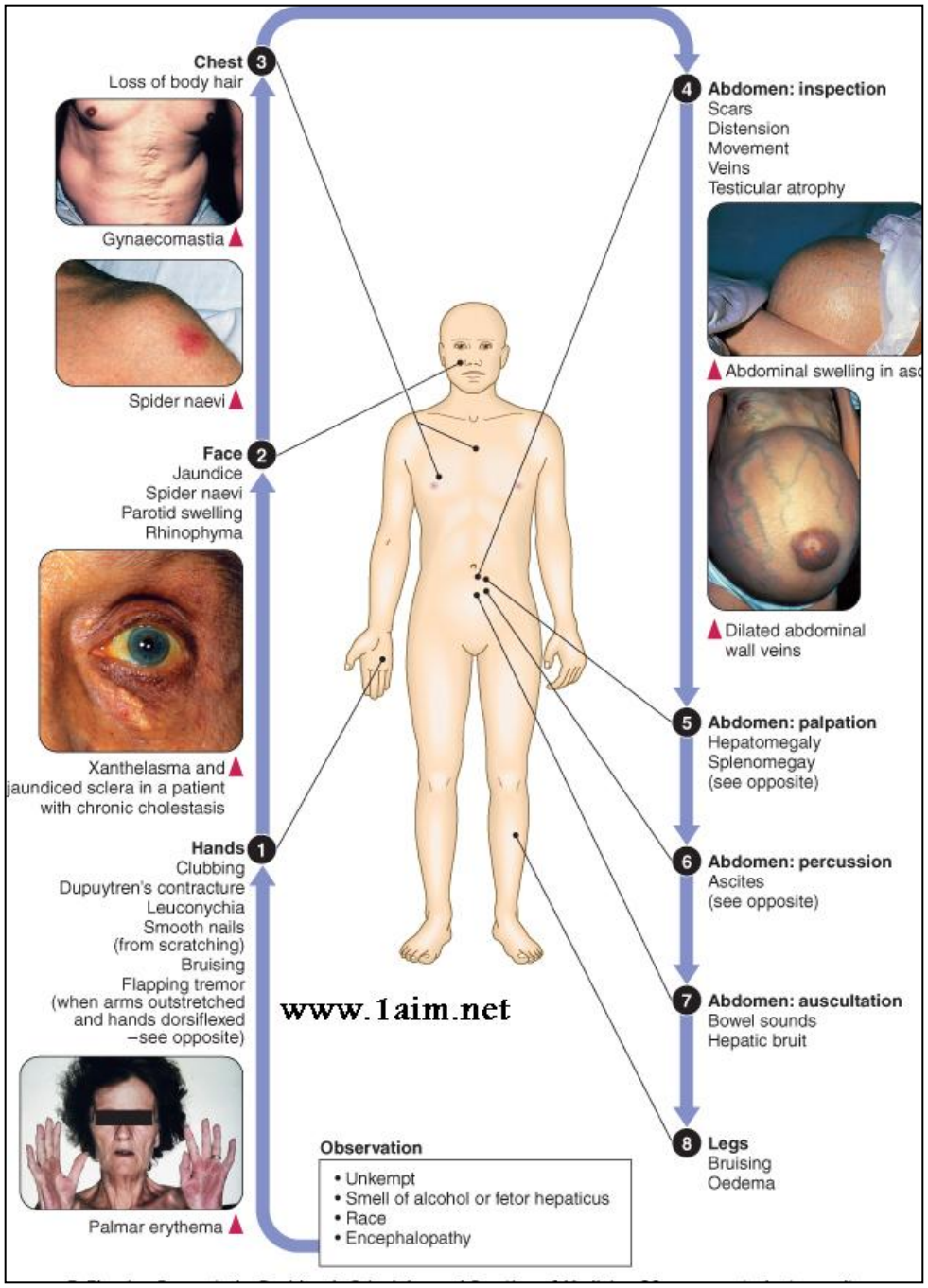
Chronic hepatitis

- 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


3 Chest
Loss of body hair
Gynaecomastia
Spider naevi
2 Face
Jaundice
Spider naevi
Parotid swelling
Rhinophyma
Xanthelasma and jaundiced sclera in a patient with chronic cholestasis
1 Hands
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

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

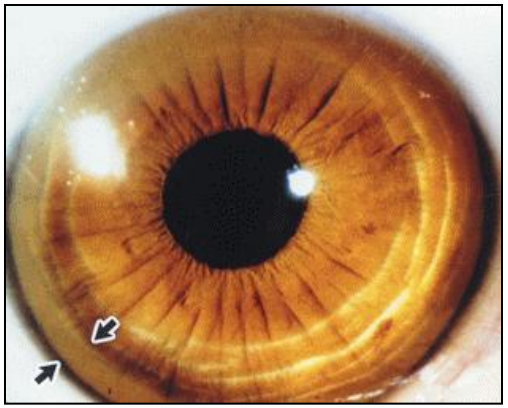
- Other autoimmune diseases may coexist, including thyroiditis, diabetes
- Dx:
  - High transaminases (ALT & AST> GGT& ALP) +
  - High serum gamma globulin concentrations
  - Liver biopsy

- Rx: Immunosuppressive medications e.g.: steroids….

Wilson disease

- 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 extrahepatic manifestations of the disease.



- Wilson disease SHOULD be included in the differential diagnosis of any child who presents with liver disease, neurologic abnormalities, behavioral changes

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 chelation of copper with penicillamine, which allows for its excretion into the urine (early diagnosis = better prognosis)

- It is important to consider this diagnosis in every child who has signs of chronic liver disease.

Un-conjugated hyperbilirubinemia **with normal LFTs**

- Criggler Najjar syndrome: glucouronyl transferase enzyme abscent (type 1) or deficient (type 2)…? Difference

- Gilbert syndrome: older children & adults, observed when sick or dehydrated, not need treatment

Conjugated hyperbilirubinemia **with normal LFTs**

1- Dubin Johnson syndrome

2- Rotor disease

- Present with jaundice at any age, mild
- Not require treatment

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

Reference

- Ian D. D'Agata and William F. Balistreri. *Pediatr. Rev. 1999;20;376*

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