Liver disease in children

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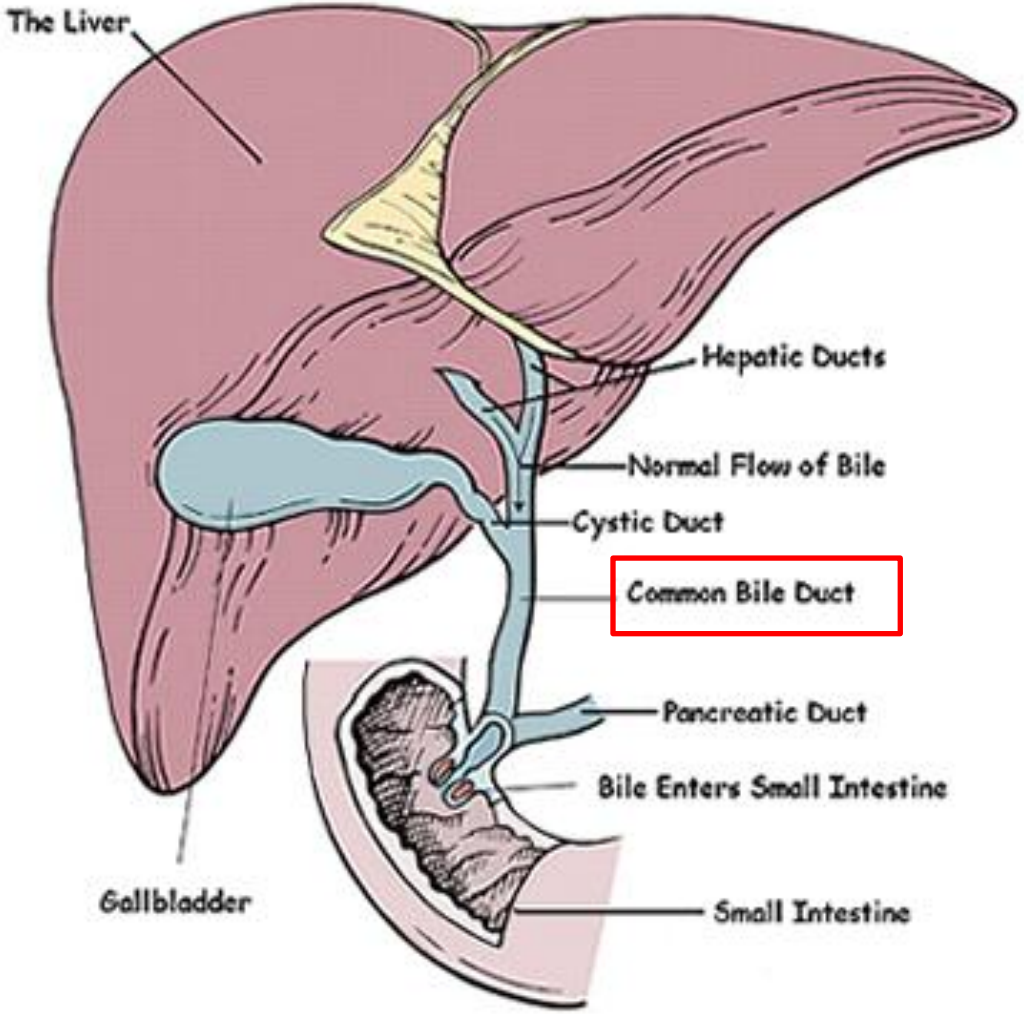
PART - 1

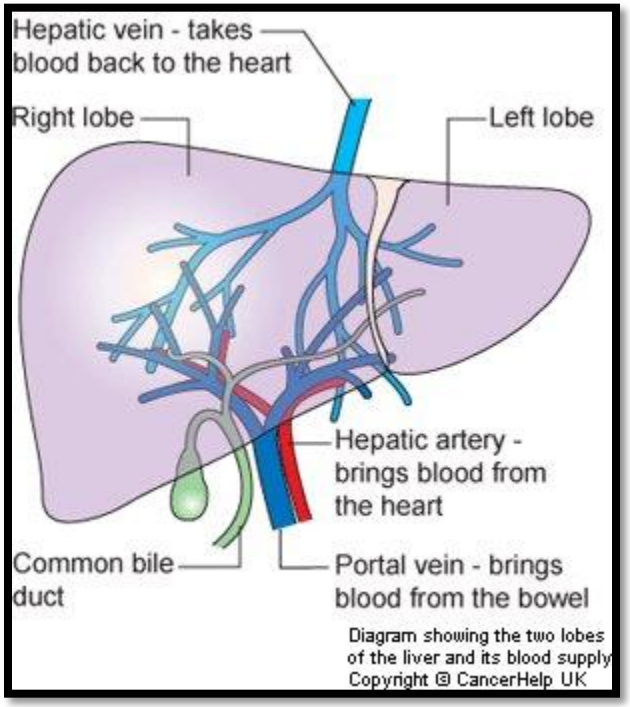
NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

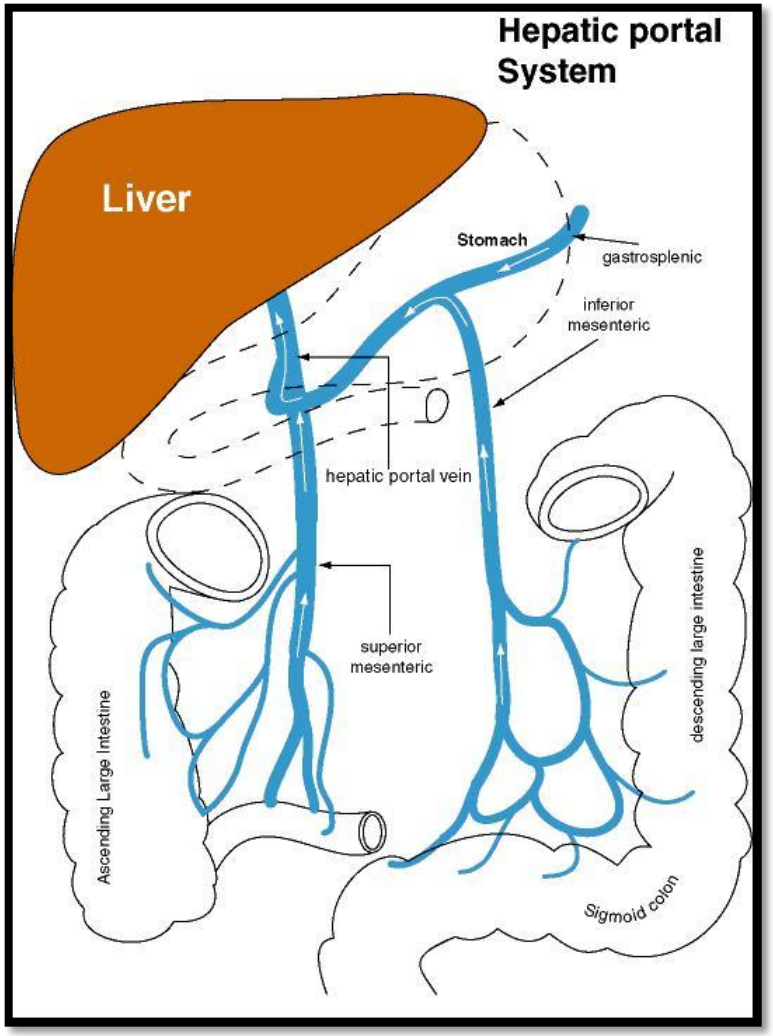
Liver anatomy



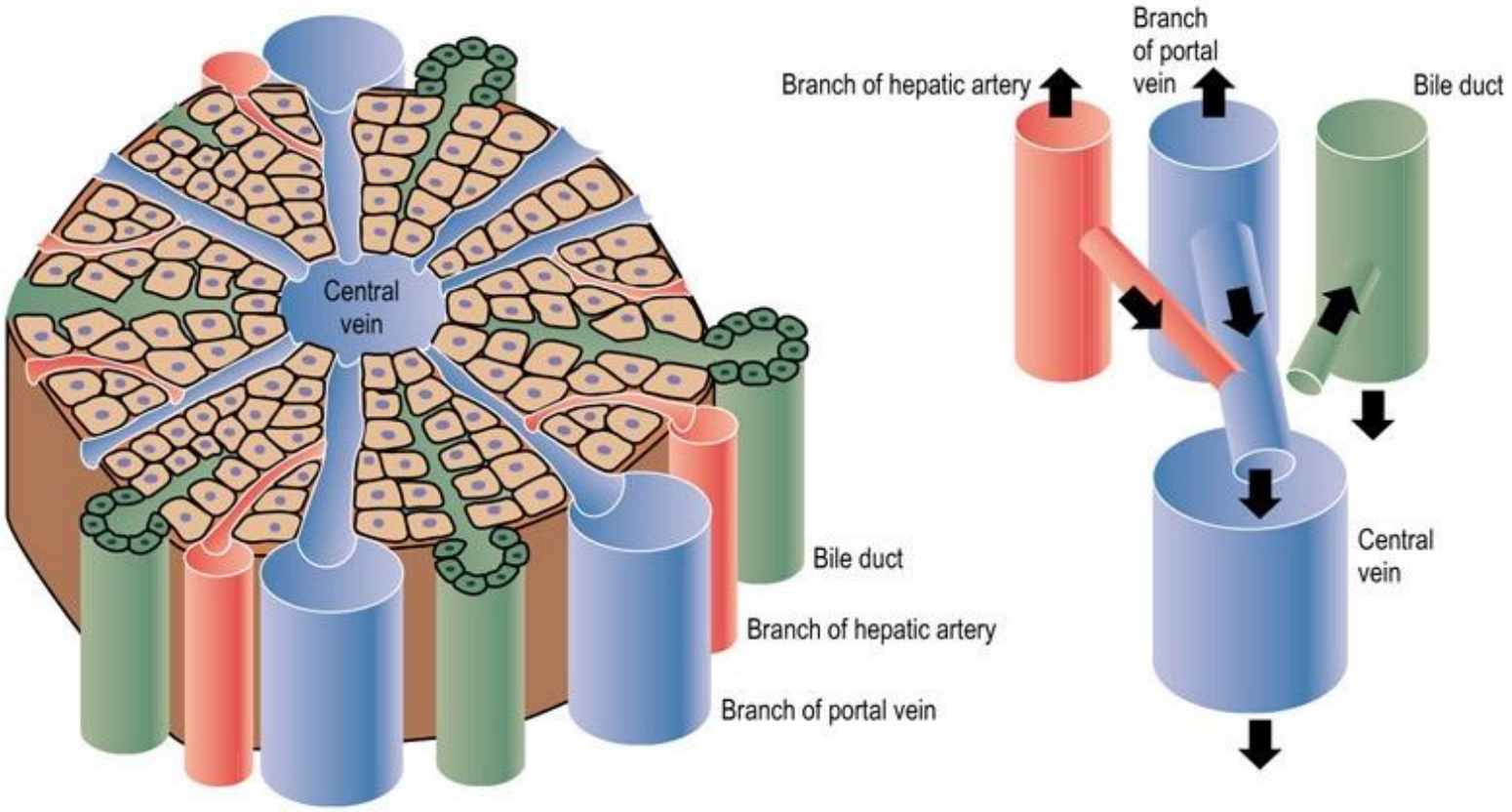
Liver blood supply

- Liver has **<u>dual Blood supply</u>** resources ;
- 70% from portal vein and 30% from Hepatic artery

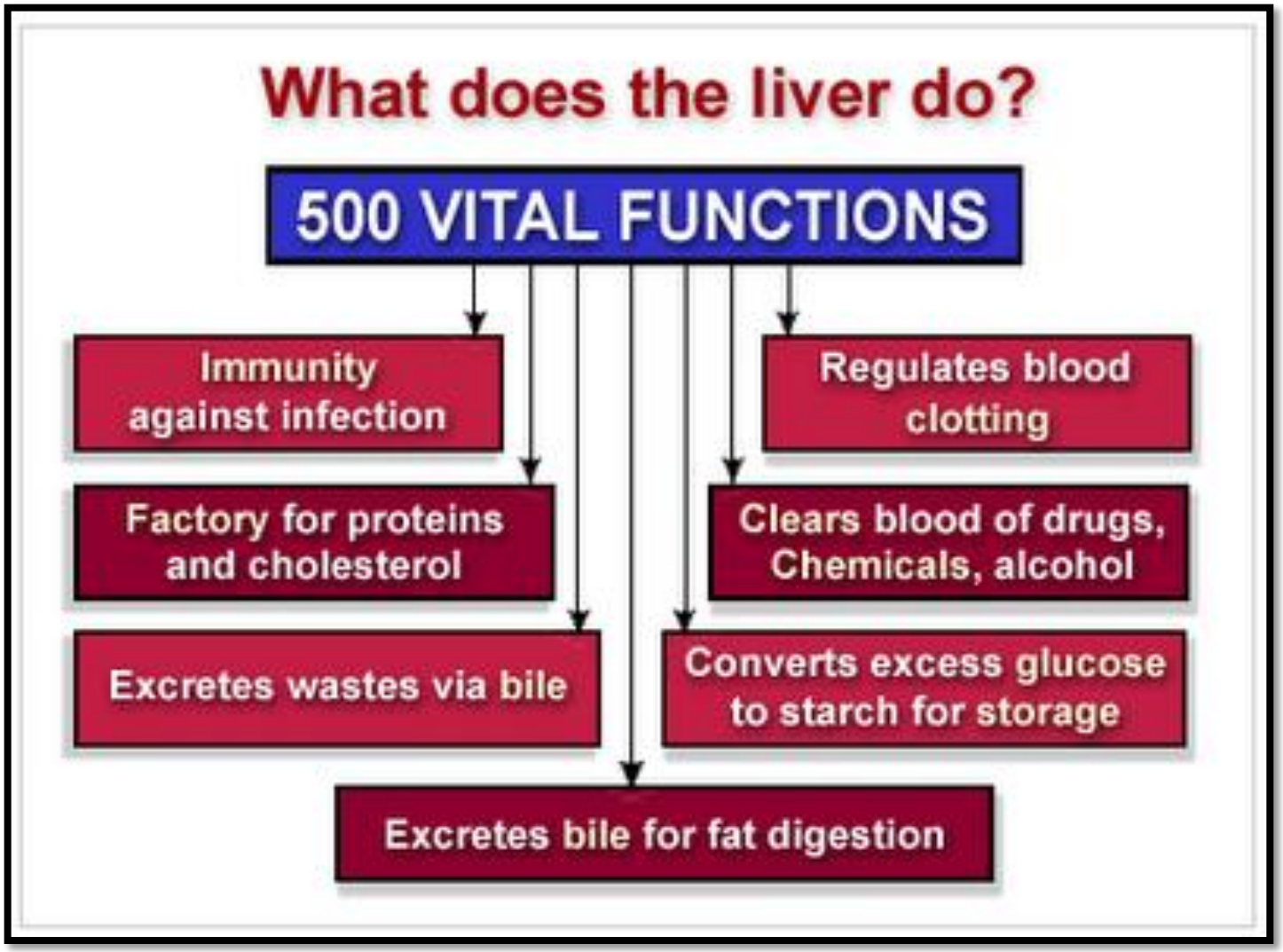




Liver Histology



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:

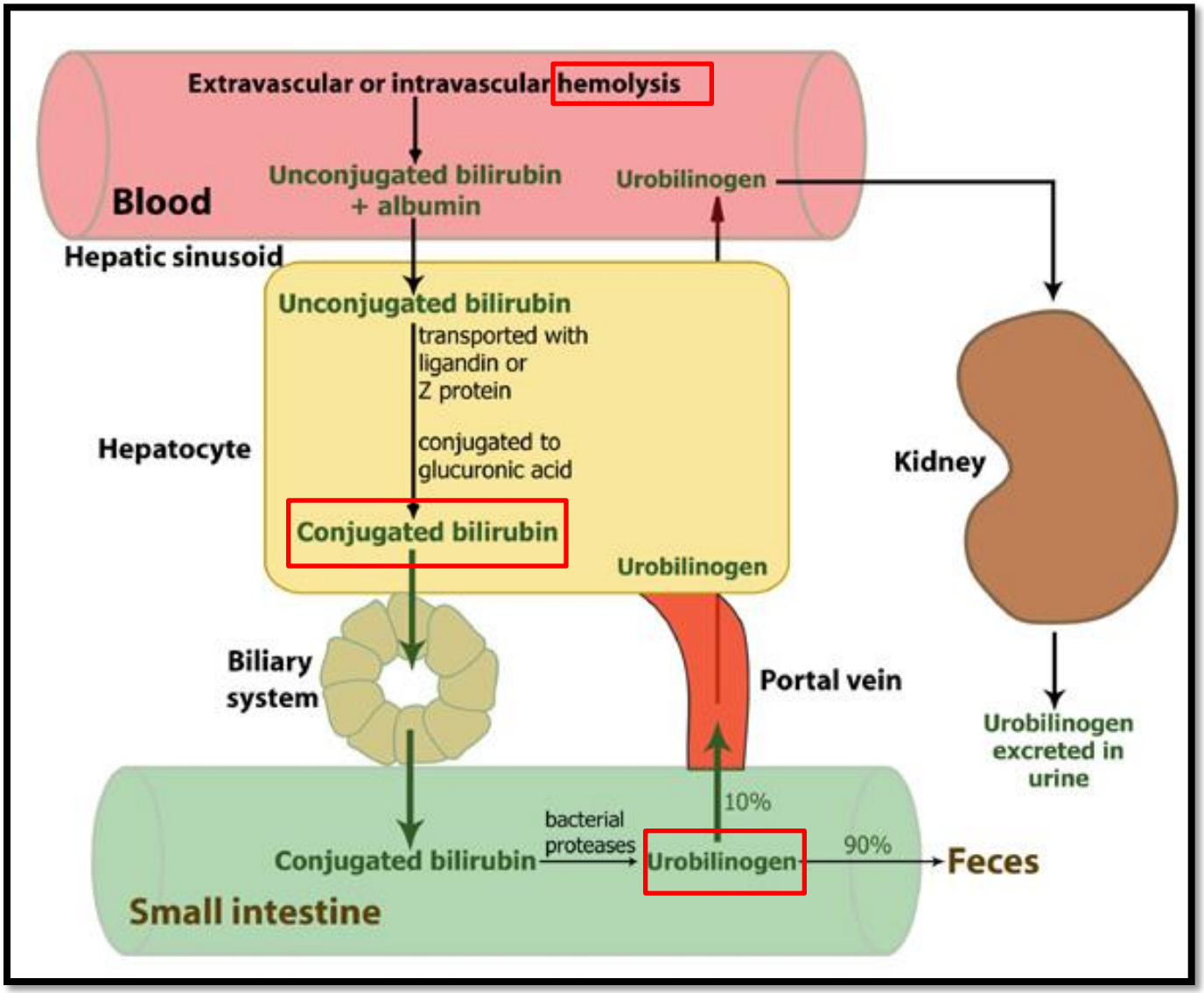
  GGT /ALP > AST/ALT

  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:** Wilson disease, Auto-immune hepatitis

- **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 # jundice

- 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) →….

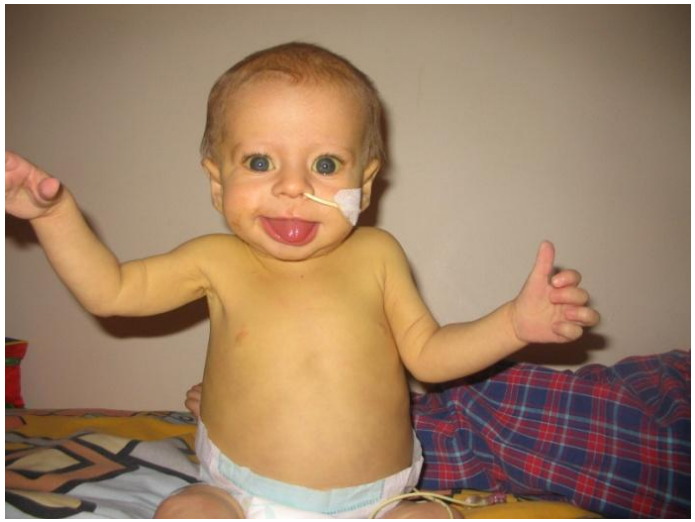
Presentation of cholestasis

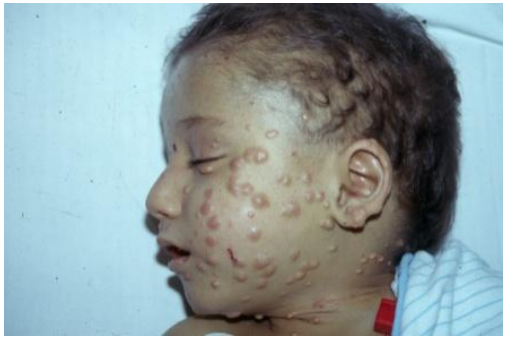
- **Jaundice** (accumulation of conjugated bilirubin)

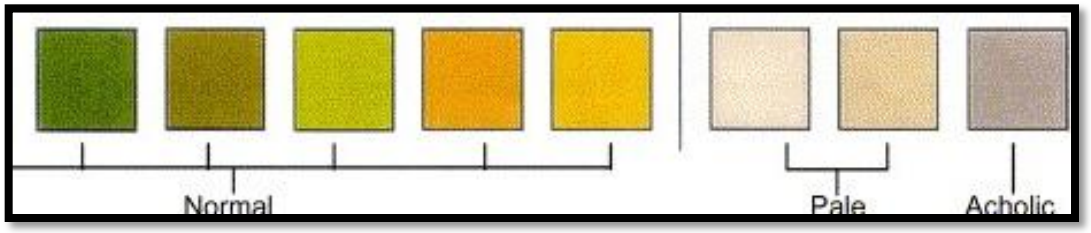
- **Pale stool (Acholic stool)… Why??**
- **Dark and foamy urine** (bile salts in the urine)
- **Pruritis** (accumulation of bile salts under the skin)
- **Xanthomas depositions** (accumulation of cholestrol)

- Hepatomegaly +/- Splenomegaly
- Failure to thrive (FTT)/ poor weight gain
- Incidental lab finding

Signs of cholestatic liver disease







Evaluation of infants with cholestatic liver disease

- Confirm cholestasis
  - —Clinical evaluation (family history, feeding history, physical examination)
  - —Fractionation of serum bilirubin and determination of serum bile acid levels
  - —Assessment of stool color
  - —Index of hepatic synthetic function (prothrombin time and albumin)
- Recognize specific entities
  - —Viral and bacterial cultures (blood, urine, cerebrospinal fluid)
  - —Hepatitis B surface antigen and other viral and syphilis (VDRL) titers in selected, high-risk patients
  - —Metabolic screen (urine-reducing substances, urine and serum amino acids)
  - —Thyroxine and thyroid-stimulating hormone
  - —Alpha 1-antitrypsin phenotype
  - —Sweat chloride
  - —Qualitative analysis of urinary bile acid profile
  - —Ultrasonography
- Differentiate biliary atresia from neonatal hepatitis
  - —Hepatobiliary scintigraphy or duodenal intubation for bilirubin content
  - —Liver biopsy

Hepato-cellular 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***

- 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 & CHILDREN

Biliary Atresia (BA)

- Biliary atresia is an obstruction disease of the biliary tree (mainly extra-hepatic) secondary **to idiopathic inflammatory/autoimmune process** → fibrosis and 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

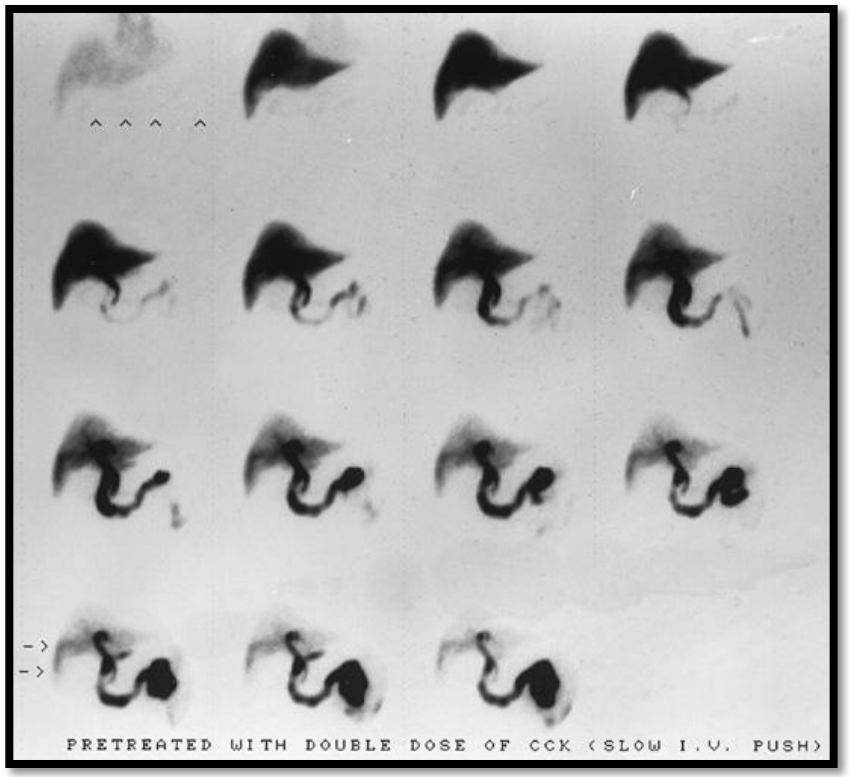
- **Abdominal US:** rule out other causes of biliary obstruction (choledochal cyst, GB stones…)

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

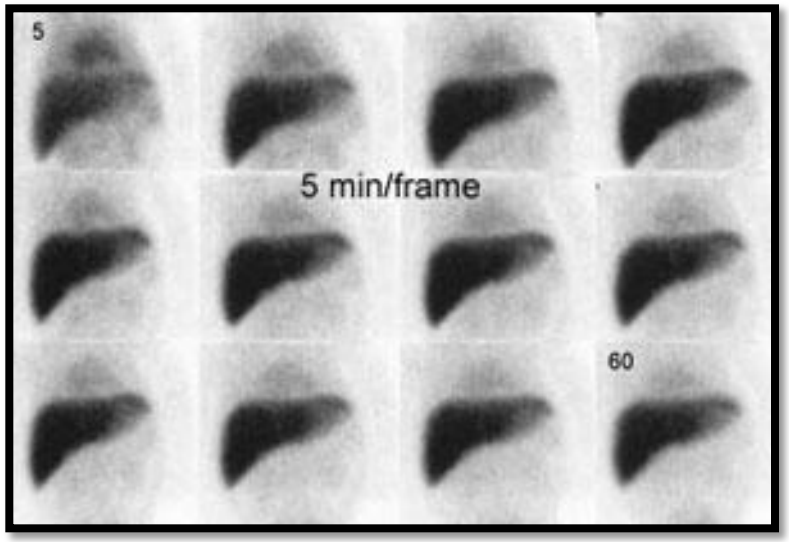
  shows good uptake of tracer and no excretion of it into the intestine, even 24 hours later.

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

Hepato-biliary scintigraphy (HIDA scan)

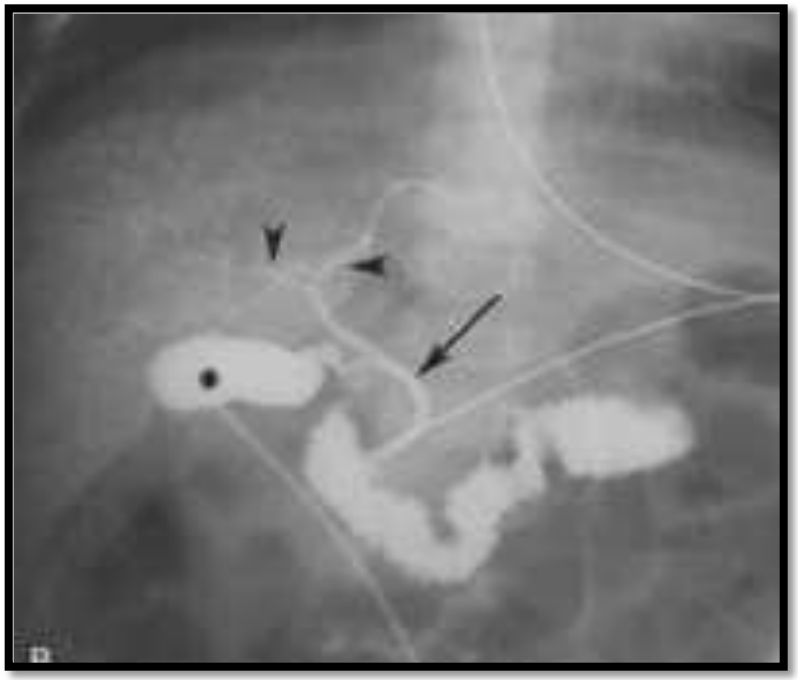


NORMAL HIDA SCAN

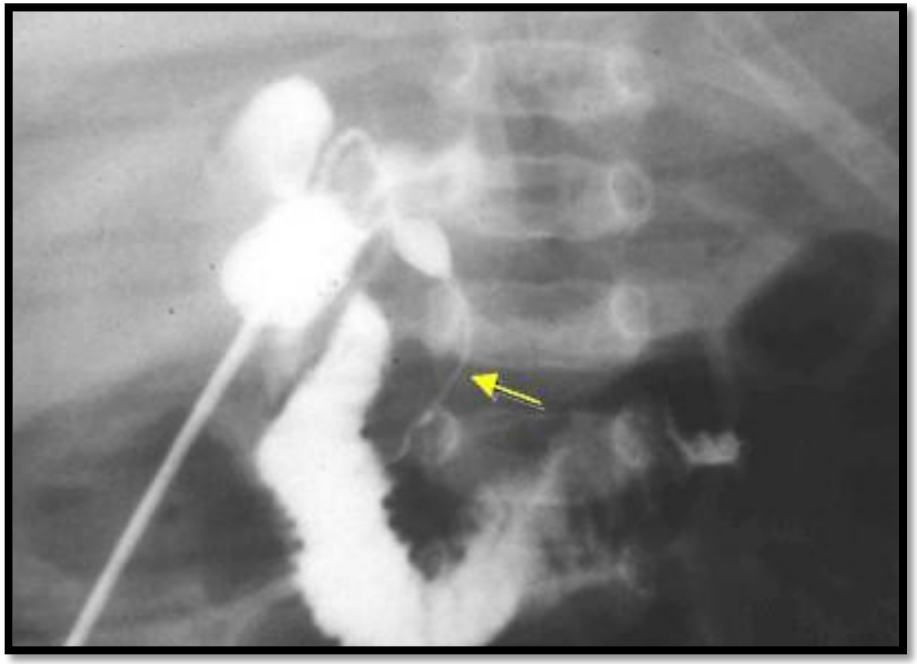


HIDA scan in BA patient

Definitive diagnosis is confirmed by Intra-operative cholangiogram



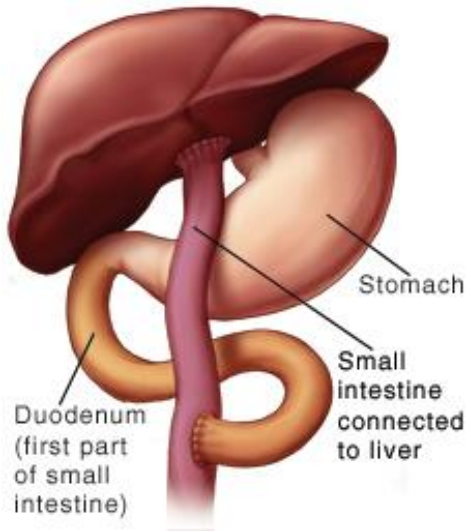
Normal study



Abnormal study
(hypoplastic common bile duct)

BA Management

- **Surgical correction (Kasai porto-entero-stomy) :**
- Should be done before 2 months of age (MCQ) (after that increase risk of fibrosis & subsequent cirrhosis)

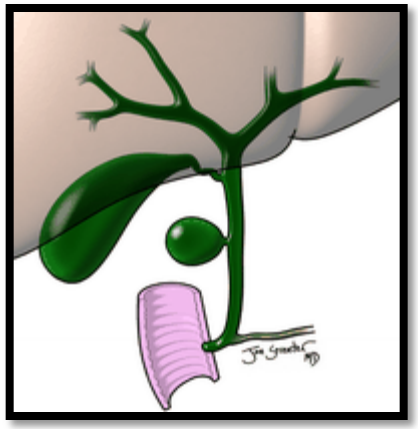


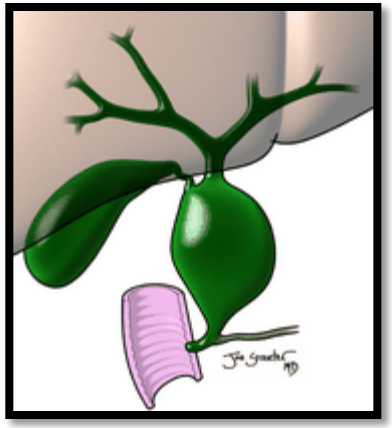
- **Liver transplantation** if Kasai failed, or if late presentation (> 3 months), or picture of decompensated liver disease

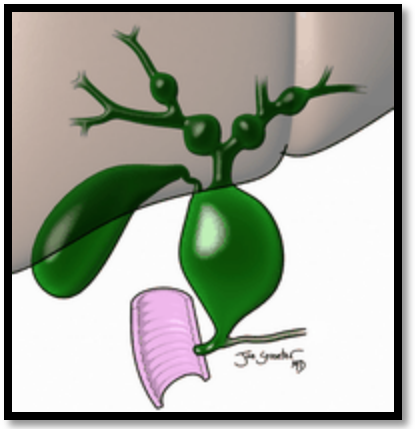
Choledocal cyst

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

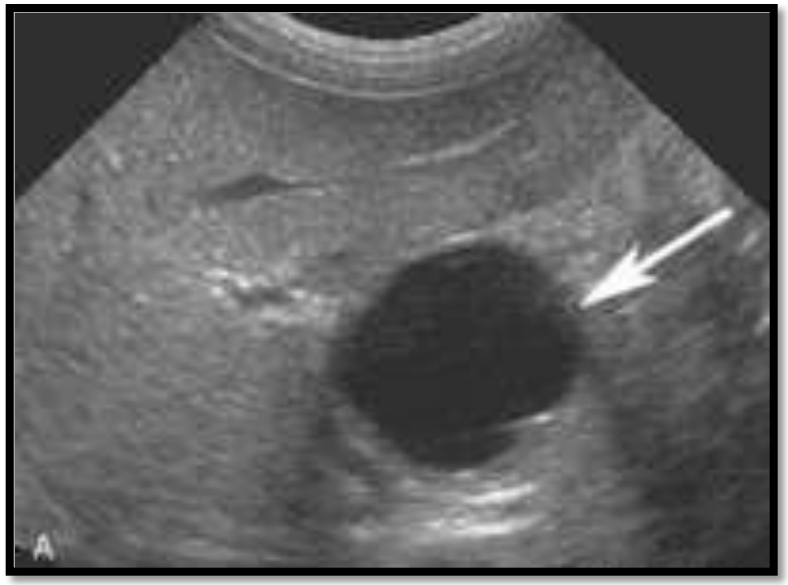
- Present with cholestasis picture, abdominal mass or asymptomatic, or biliary carcinoma in adults







Choledocal cyst



Treatment: surgical excision

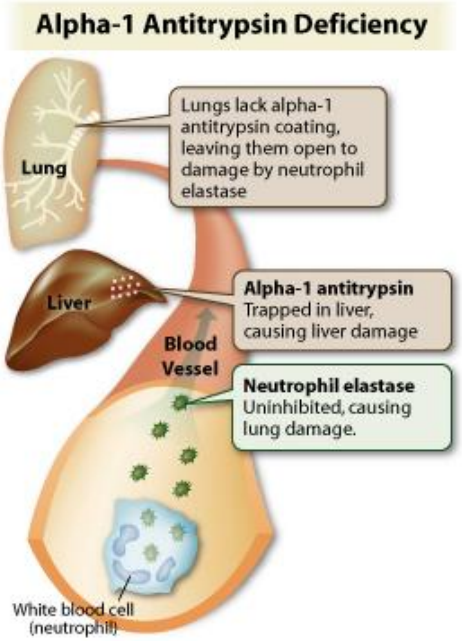
Alpha-1 Antitrypsin deficiency

- A-1 AT is a protease (elastase, trypsin) inhibitor that protect lung from neutrophil elastase destruction

- AR disease
- Abnormal mutation (Pi MM→ Pi ZZ →**form abnormal A-1 AT protein**→ failed excretion from liver (trapped) → cholestatic liver disease
- Lung disease is very rare in children

- **Dx: A-1 AT level & phenotyping (pi ZZ)**

- **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)
- Important to R/O obstructive disease like BA(time is crucial)
- Management of these infants involves supportive measures till specific cause found

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)**
- ***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
- The disease typically is self-limited in children and often is clinically not clear
- No chronic carrier state is identified.
- 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

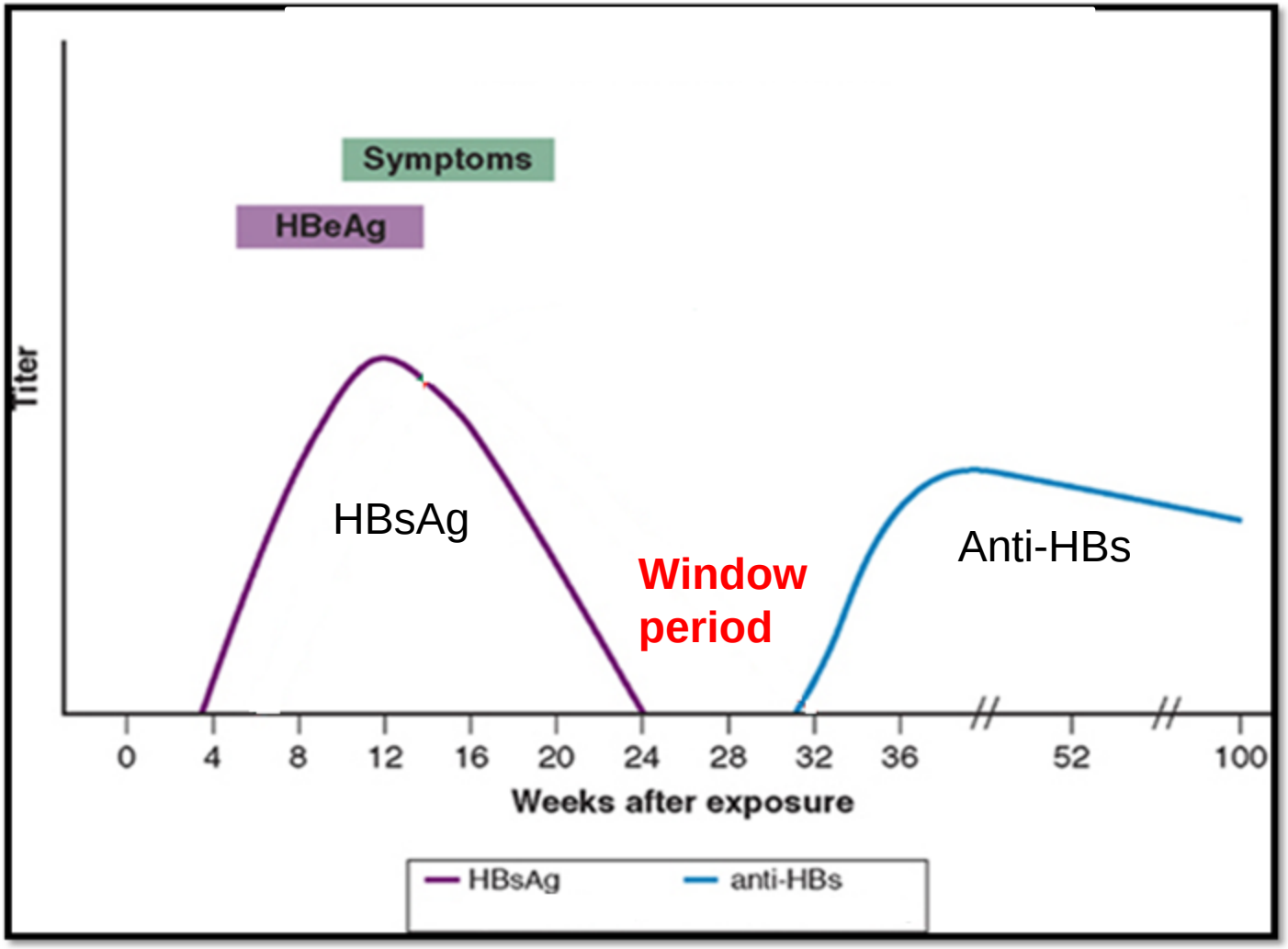
Hepatitis B

- Hepatitis B virus (HBV) infection can cause both acute and chronic hepatitis
- It can progress to cause **cirrhosis and hepatocellular carcinoma** if not treated well
- Risk of transmission…..primarly vertical (mother to baby) in children or via contaminated blood

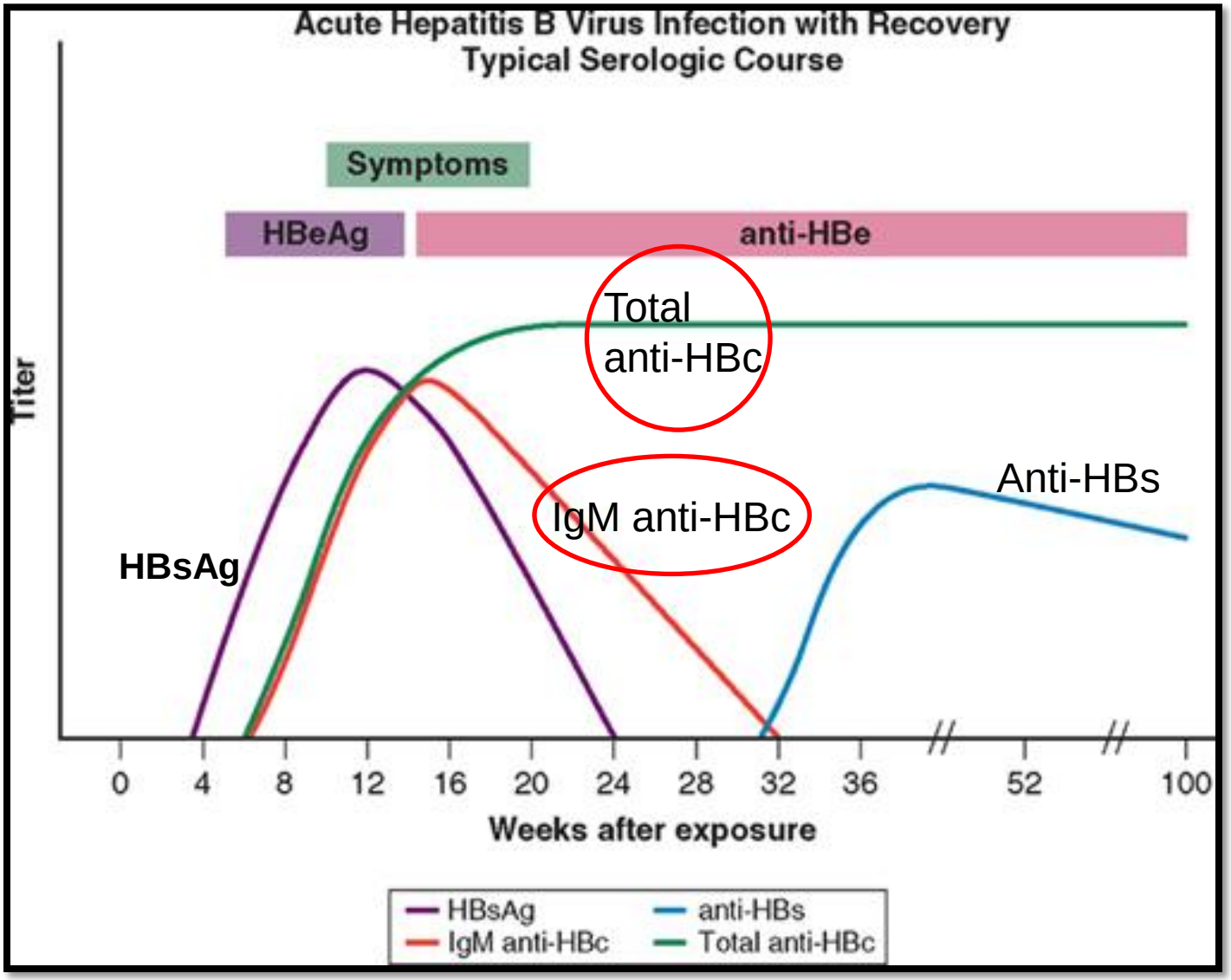
- **Diagnosis** rests on the demonstration of hepatitis B surface antigen (HBsAg)

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

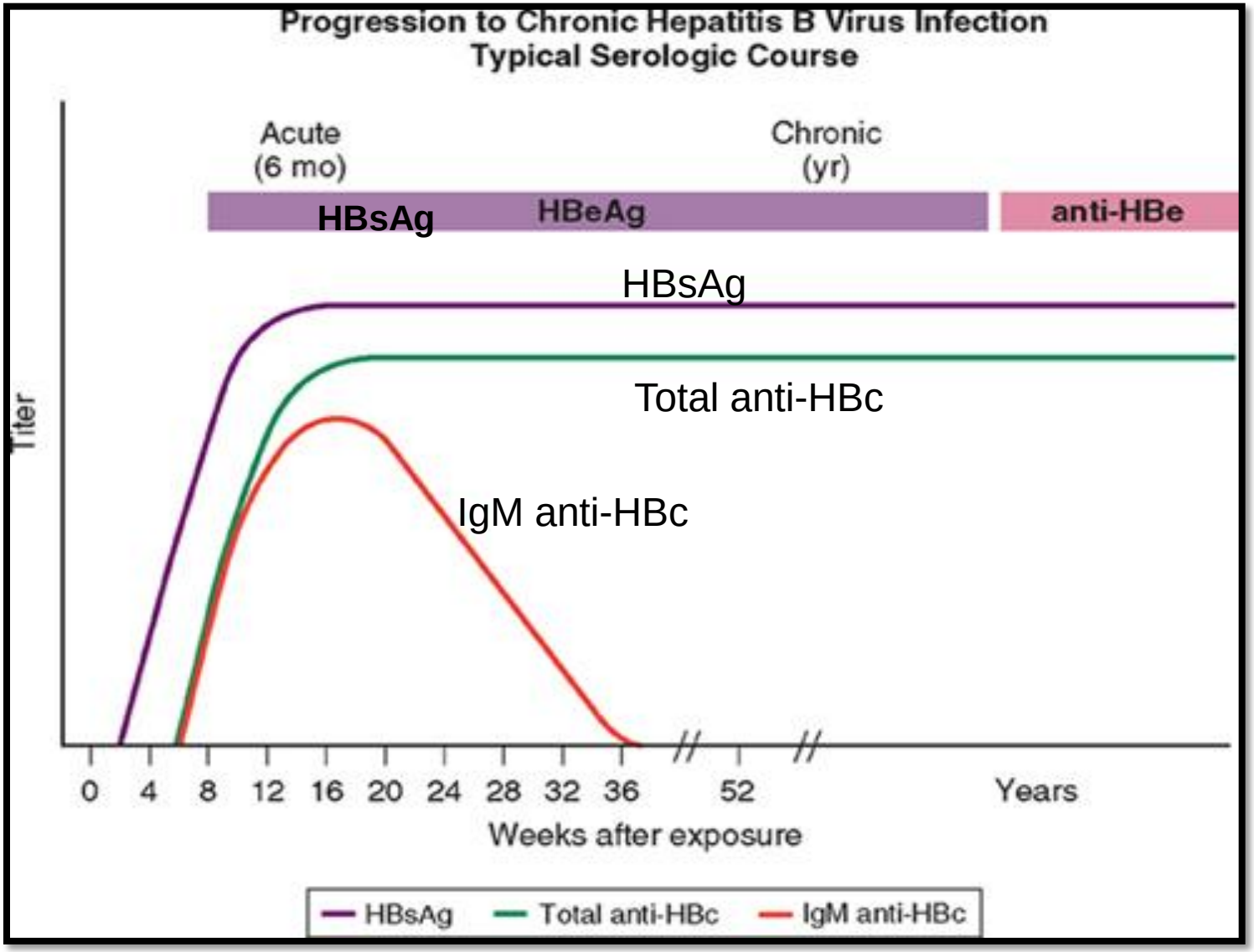
HBV serology markers



HBV serology markers.. immunity



Chronic hepatitis



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:**
  - 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 & see**

Hepatitis C

- Hepatitis C virus (HCV) causes acute hepatitis, which **progresses to chronic disease**

- End-stage liver disease can occur in up to 10 %, but 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…..

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

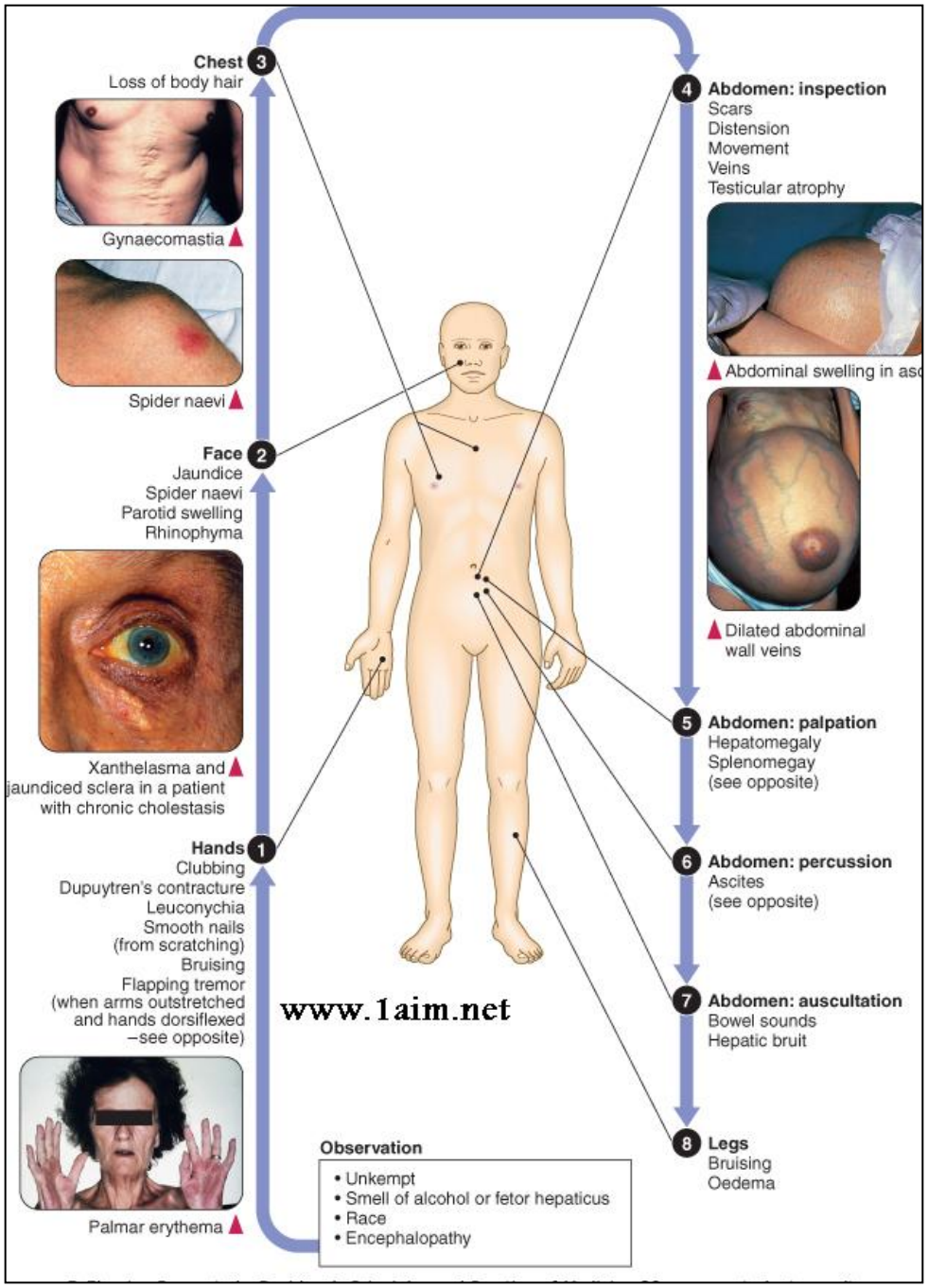
Chronic hepatitis

- 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; an 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
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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

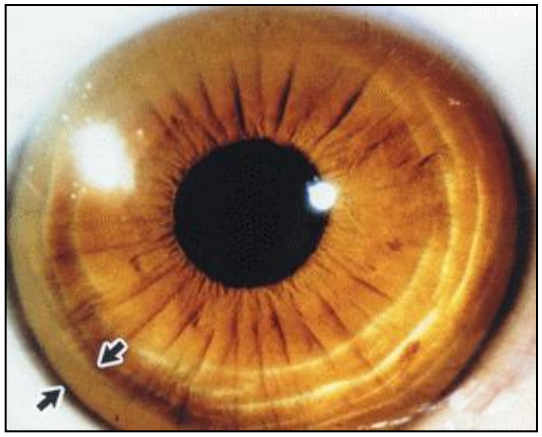
- Other autoimmune diseases may coexist, including thyroiditis, diabetes
- Dx:
  - High transaminases (ALT & AST> GGT& ALP) +
  - Serum gamma globulin concentrations are elevated in nearly all patients
  - Liver biopsy
- Rx: Immunosuppressive medications e.g.: steroids….

Wilson disease

- AR disorder
- caused by a defect in biliary copper excretion, in which excessive copper accumulation in the liver leads to cirrhosis.

- The excess copper is deposited in the 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, or Kayser-Fleischer rings.



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

- Because the prognosis depends on early treatment and individual responsiveness to chelation therapy, 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

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 4. Diseases Causing Hepatomegaly

Infants and Children

- Storage disorders
  - —Acute: Reye syndrome (fat)
  - —Chronic: glycogenoses, mucopolysaccharidoses, Gaucher disease, Niemann-Pick disease, gangliosidosis, Wolman disease
- Nutritional problems: total parenteral alimentation (caloric overload), kwashiorkor, diabetes
- Infiltrative disorders: leukemia, lymphoma, Langerhans cell histiocytosis, granulomas (sarcoidosis, tuberculosis)
- Congenital hepatic fibrosis
- Tumors
  - —Primary: hepatoblastoma, hematoma, hemangio-endothelioma
  - —Metastatic: neuroblastoma, Wilms tumor, gonadal tumors

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