السلايدز ممتازة والدكتور بنفسه مسوي هايلات لأهم الأشياء، النوتز هنا مجرد استزادة لا أكثر

Liver disease in children

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Objectives

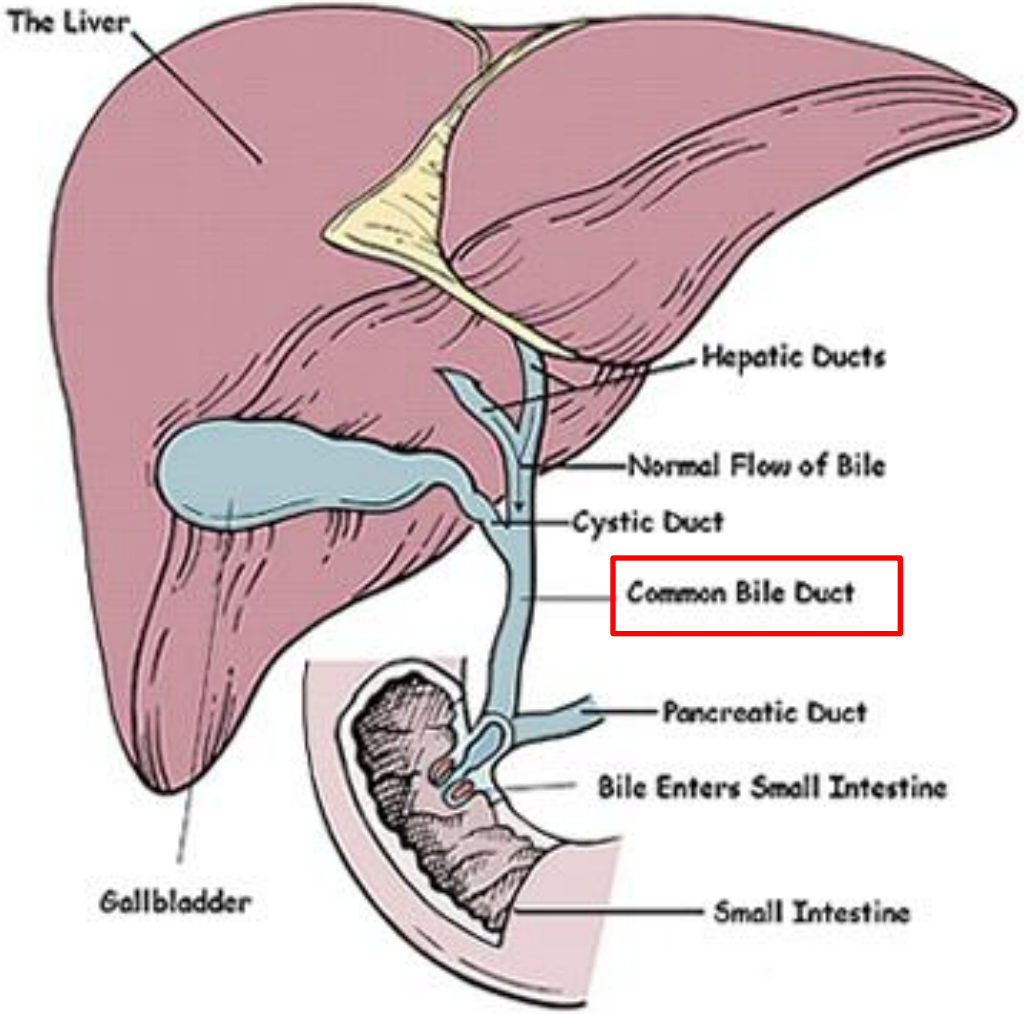
- To understand the anatomy & physiology of liver & biliary tree
- To be able to read & interpret the basics of liver function tests
- To be able to recognize the variable presentations of acute & chronic liver disease

- 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

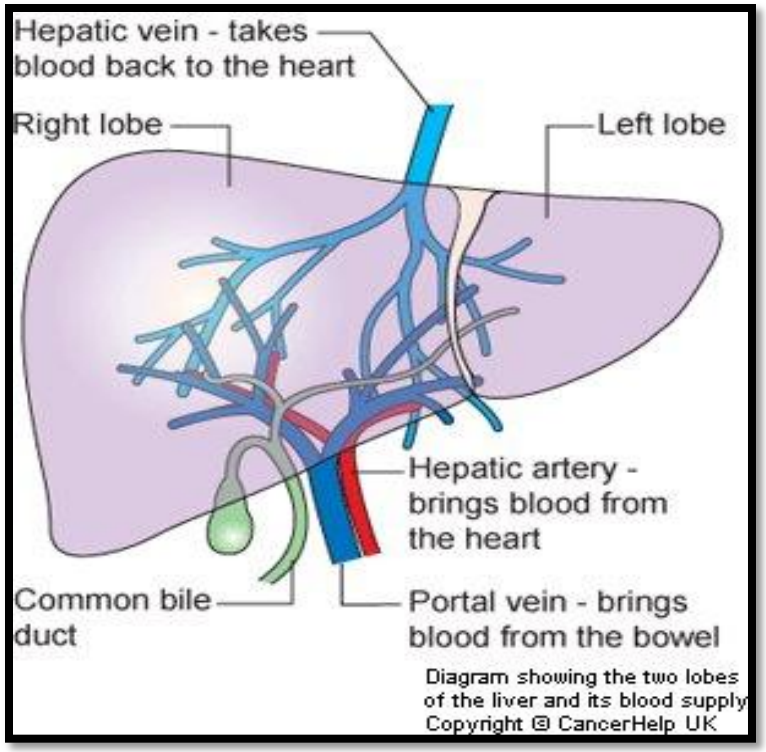
Liver anatomy

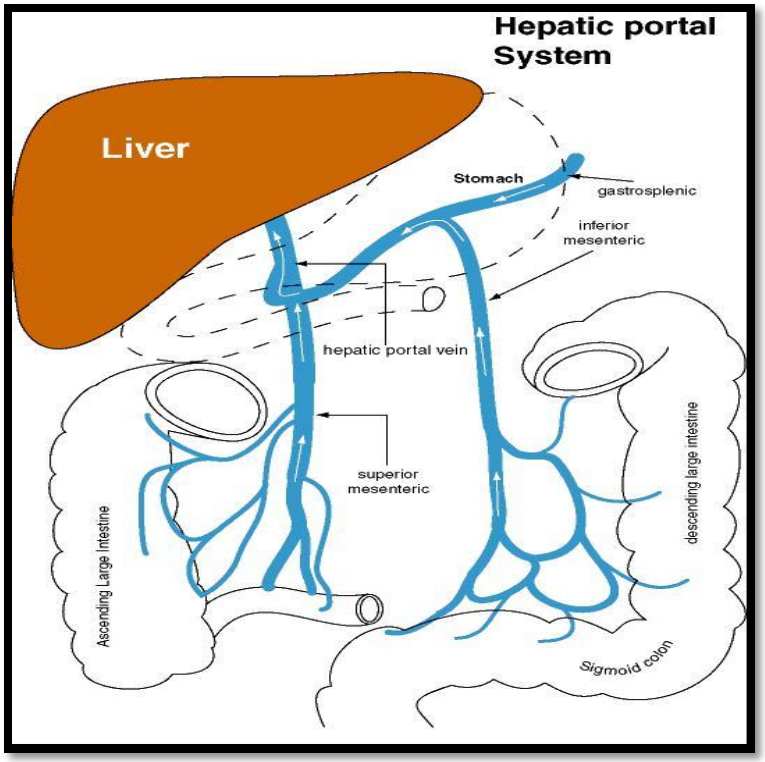


Liver blood supply

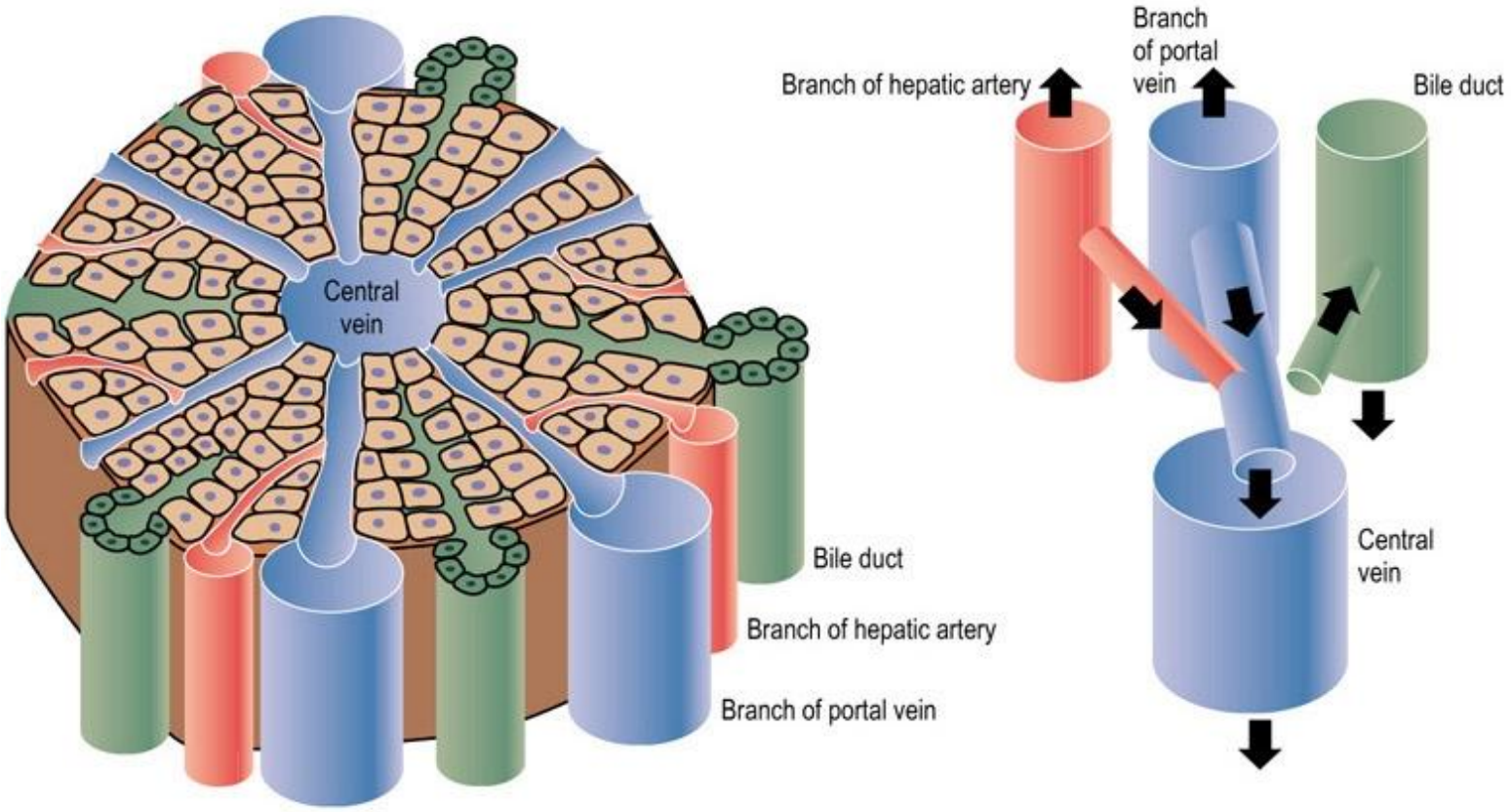
- Liver has **dual (bouble) Blood supply** resources ;
  - 70% from portal vein (nutrients)
  - 30% from Hepatic artery (oxygenated blood)

the liver is the last organ to be affected in hypovolemic shock





Liver Histology



Liver FUNCTIONS

Synthetic Function

1- Glucose (either by excess sugar storage or from glycongen)

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

L = liver specific compared to AST, AST can be secreted from RBCs or muscles. so if we found that AST is more than ALT, it could be not a liver source

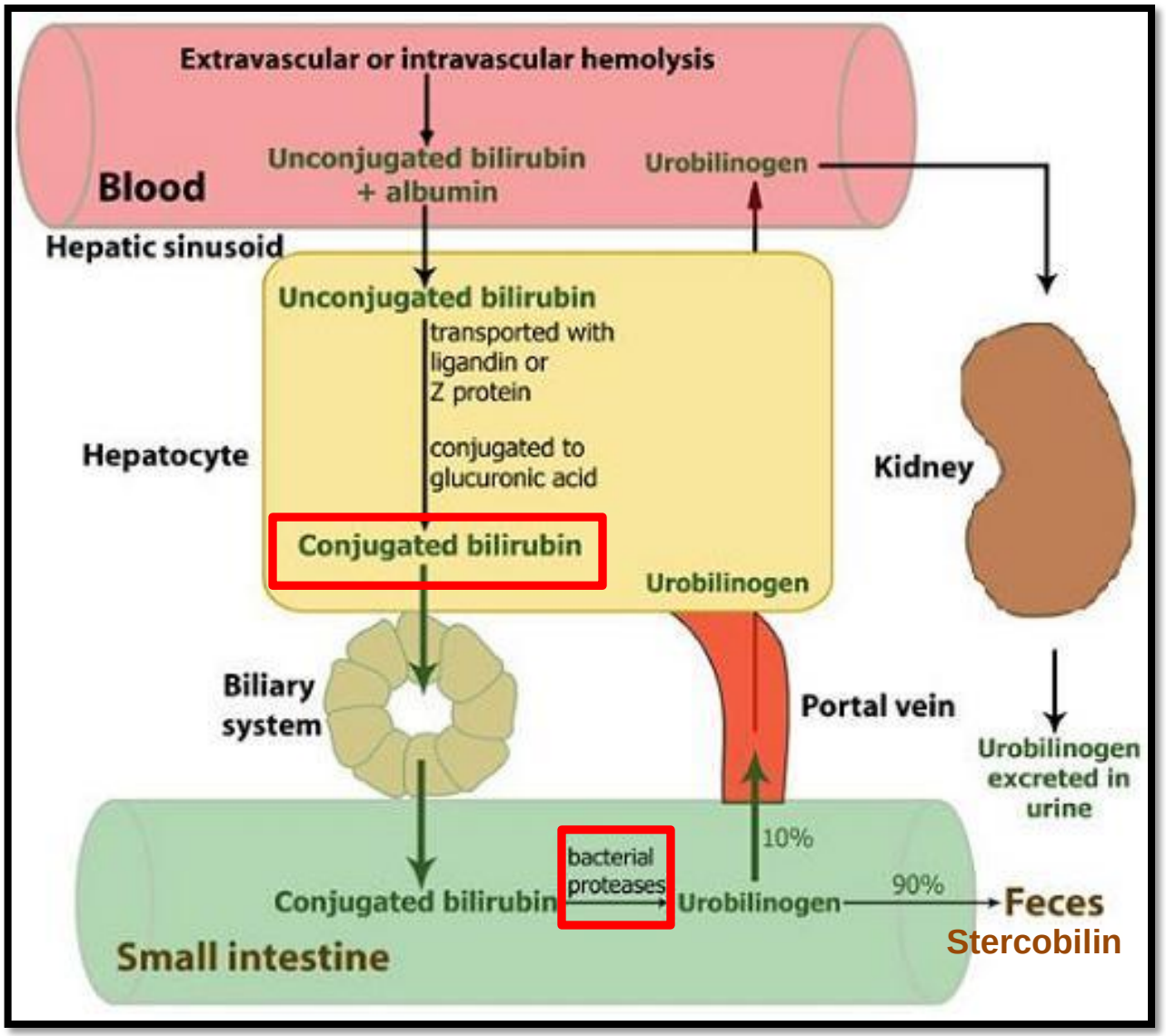
GGT is more specific compared to ALP in children, since ALP is high by default, because it secreted from their growing bones

And as you know:
- ALT and AST are secreted form hepatocytes = liver function.
- GGT and ALP are cholestatic markers = cholestasis.

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

Bilirubin metabolism

unconjugated bili is lipid soluble, it can cross the BBB and causes kernicterus



Hyperbilirubinemia: (important numbers)

- The term jaundice, derived from the French word (**jaune**), meaning (**yellow**)

- Hyperbilirubinemia (HB)= **TSB > 1.5 mg/dl** (26 mmol/l)
  total serum bili

- 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 hemolysis)

Causes of un-conjugated HB (MCQs)

very important slide

Haemolysis ;

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

wilson is usually causes liver damage so high direct rather than indirect, but if there was excessive accumulation of copper inside RBCs it will cause hemolysis and high level of indirect bili

Non- haemolysis;

breast feeding = early, secondary to dehydration.
milk jaundice = 2-3 w, secondary to the milk itself.
both are mild

1- Breast feeding/Milk Jaundice

2- Criglar Najjar syndrome

3- hypothyroidism

can cause both, direct and indirect because of slow metabolism.

4- Gilbert syndrome,

5-Pyloric stenosis

Patterns for liver diseases:

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

B) Hyperbilirubenemia <u>with</u> elevated liver enzymes

C) High liver enzymes without Hyperbilirubenemia

Hyperbilirubinemia

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

both are mild, can present early or late, managed conservatively. they are fine but a bit yellow

Un-conjugated hyperbilirubinemia **with normal LFTs**

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

type 1 is more severe due to the complete absence of the enzyme, patient with type 1 needs 17 hrs daily of phototherapy, which is possible in the first weeks of life, but liver transplant is a must later on. his liver is functioning, he only needs an accessory part to replace that enzyme.

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

Patterns for liver diseases:

1*) Cholestatic or obstructive* bile duct injury

GGT /ALP > AST/ALT

2) *Hepatocellular or liver cell inj*ury:

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 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

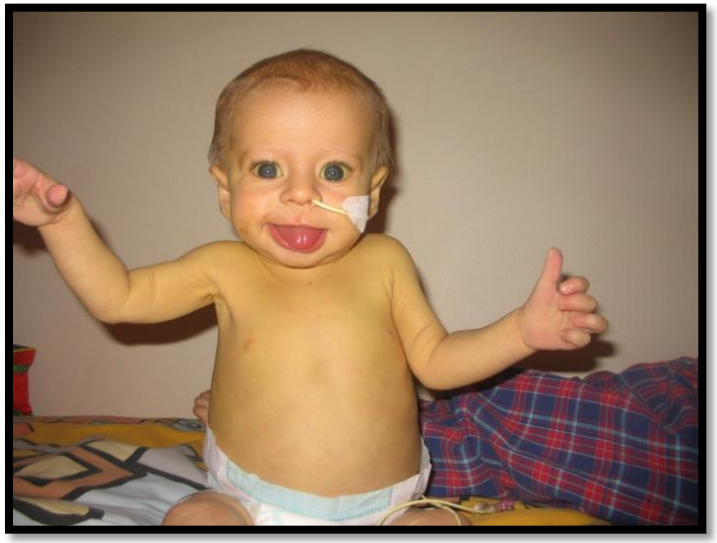
- **Cholestasis → chole= bile Stasis=stagnation**
- The obstruction of bile flow either:
  - **Mechanical block** (biliary atresia, stones…) or
  - **Functional block** (cellular receptor & transporter levels):eg:
    progressive familial intrahepatic cholestasis (PFIC) the commonest in KSA

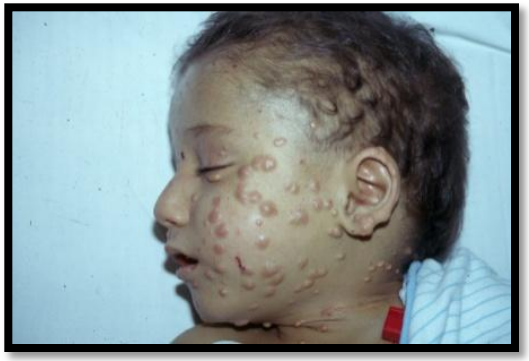
- **Cholestasis is characterized by an accumulation of compounds that cannot be excreted through the bile**
  - Conjugated/direct bilirubin→ jaundice (Cholestasis # jaundice)
  - Enzymes (ALT/AST>GGT/ALP)→ high liver enzymes in serum GGT/ALP>ALT/AST
  - Bile salts→ itchiness ithiness could be bad enough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

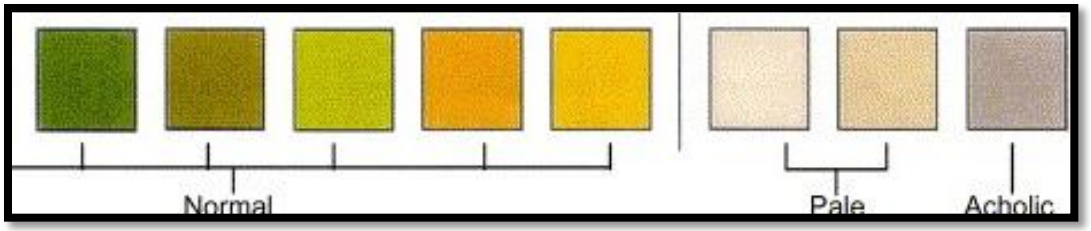
Presentation of cholestasis

- **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)

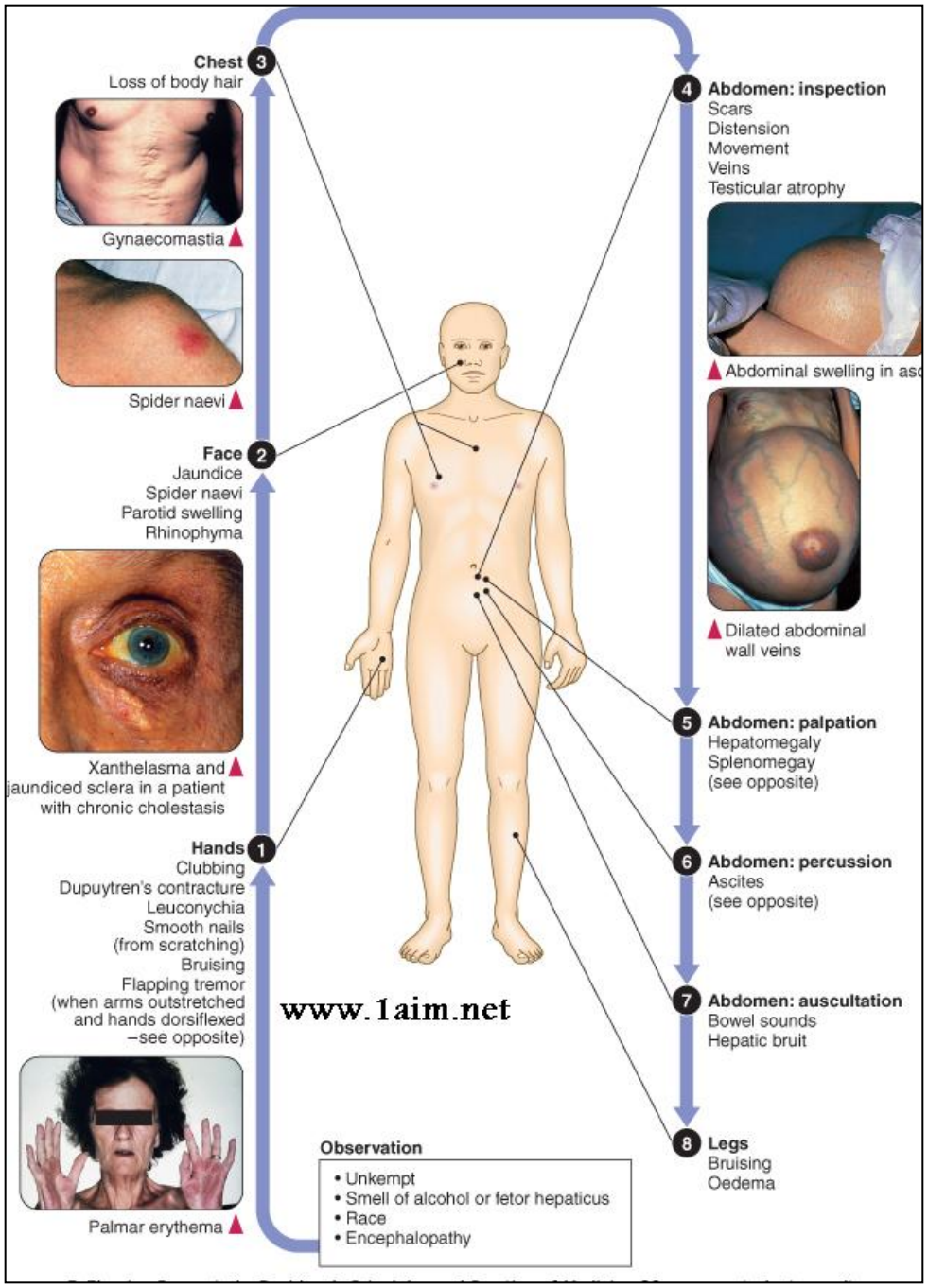
Chronic hepatitis

- **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

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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know the highlighted

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

important

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**

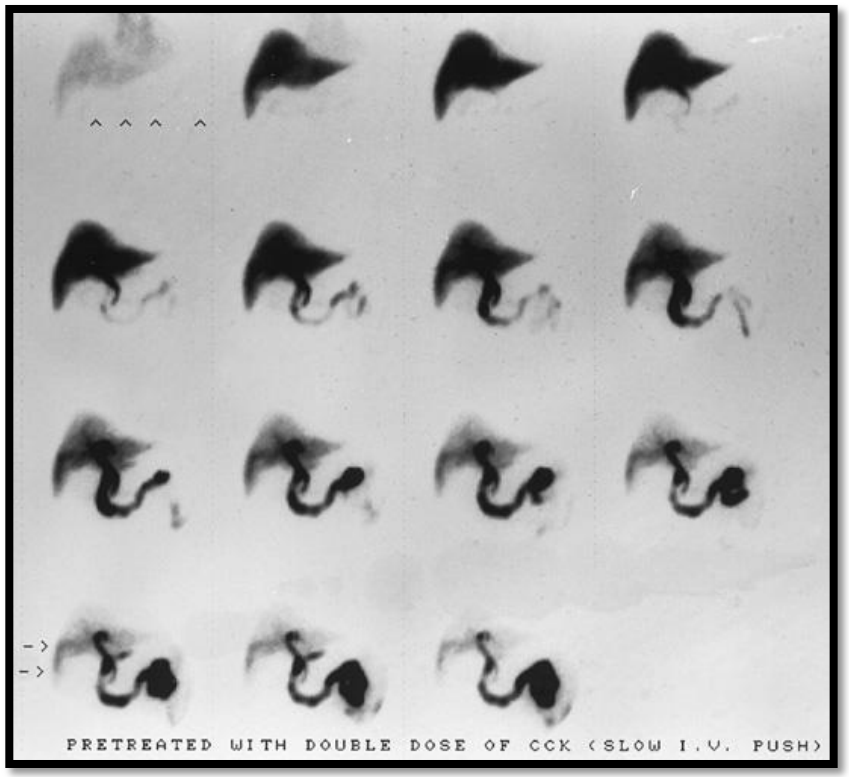
BA - Diagnosis

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

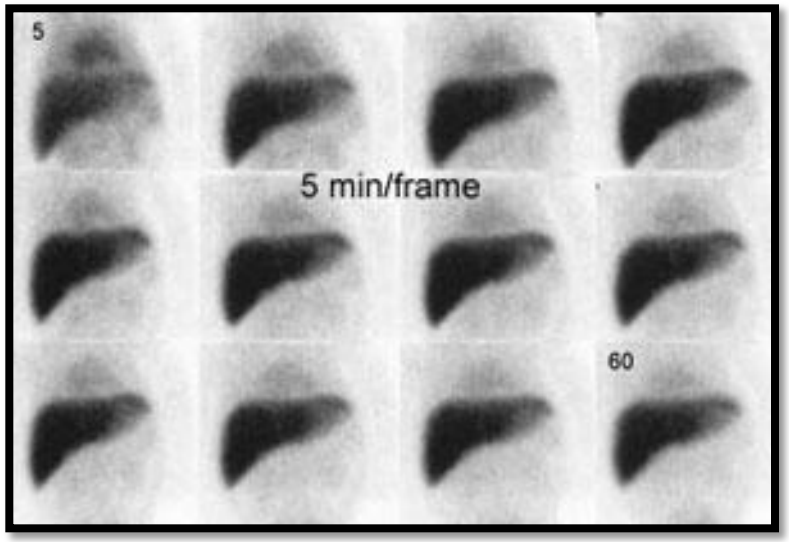
- **Abdominal US:** rule out other causes of biliary obstruction (choledochal cyst, GB stones…)

- **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



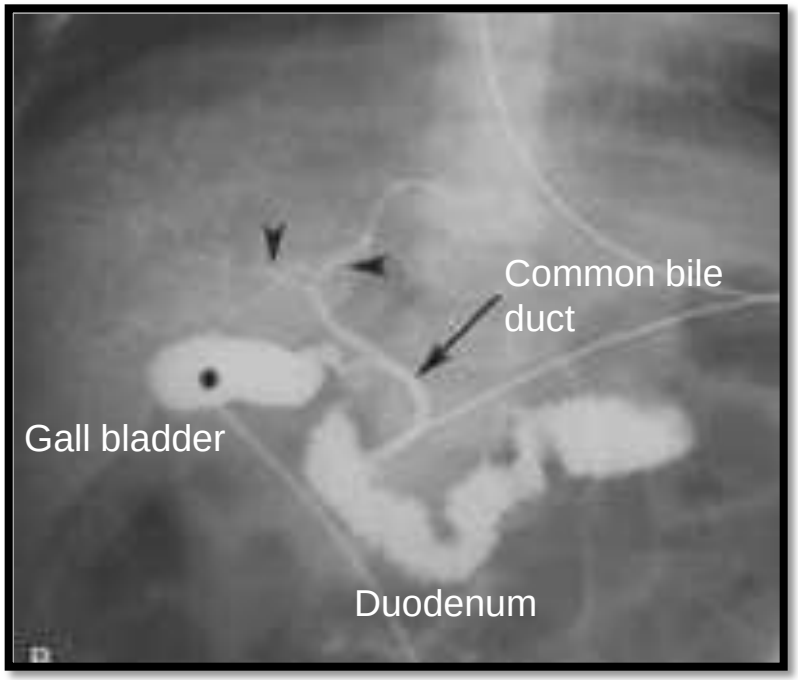
HIDA scan in BA patient

BA - Diagnosis

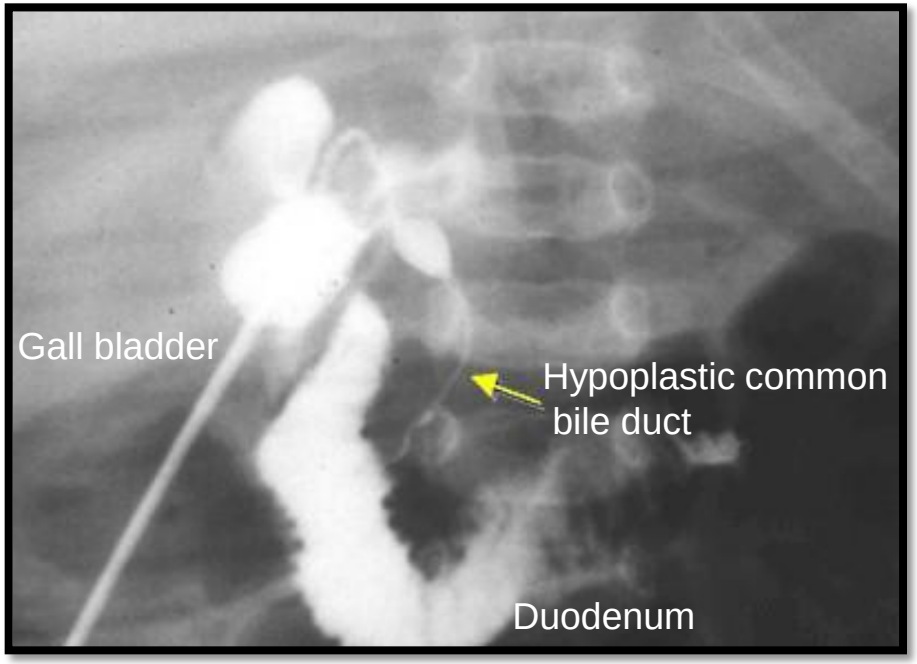
- **A liver biopsy:**
  - confirms the diagnosis by revealing characteristic findings (proliferation of the interlobular bile ducts, periportal fibrosis, and bile plugs in canaliculi and ductules)

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

Definitive diagnosis is confirmed by Intra-operative cholangiogram



Normal study



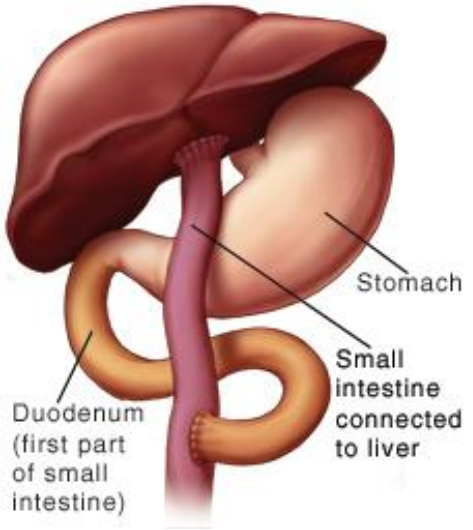
Abnormal study
(hypoplastic common bile duct)

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)

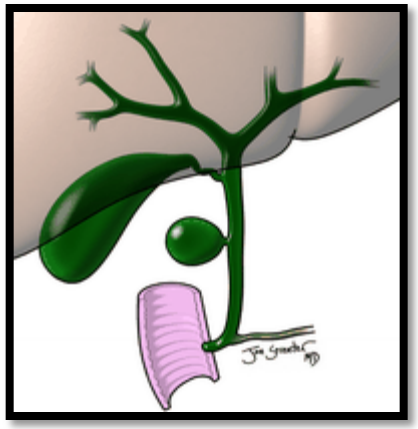
- **Liver transplantation** if:
  - Kasai failed, or
  - if late presentation (> 3 months) or
  - picture of decompensated liver disease

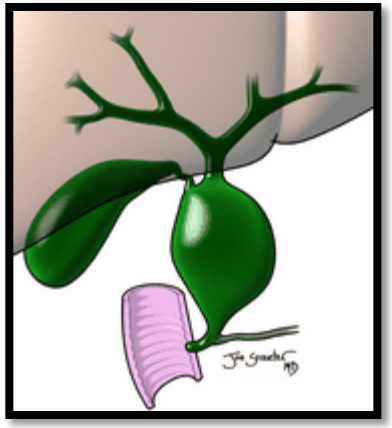


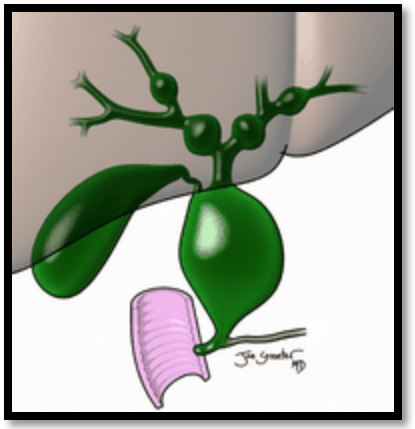
Choledocal cyst

- 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** (inhibit elastase, trypsin) → that protect lung from neutrophil elastase destruction

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

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

- Abnormal mutation causing change in the phenotype (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)

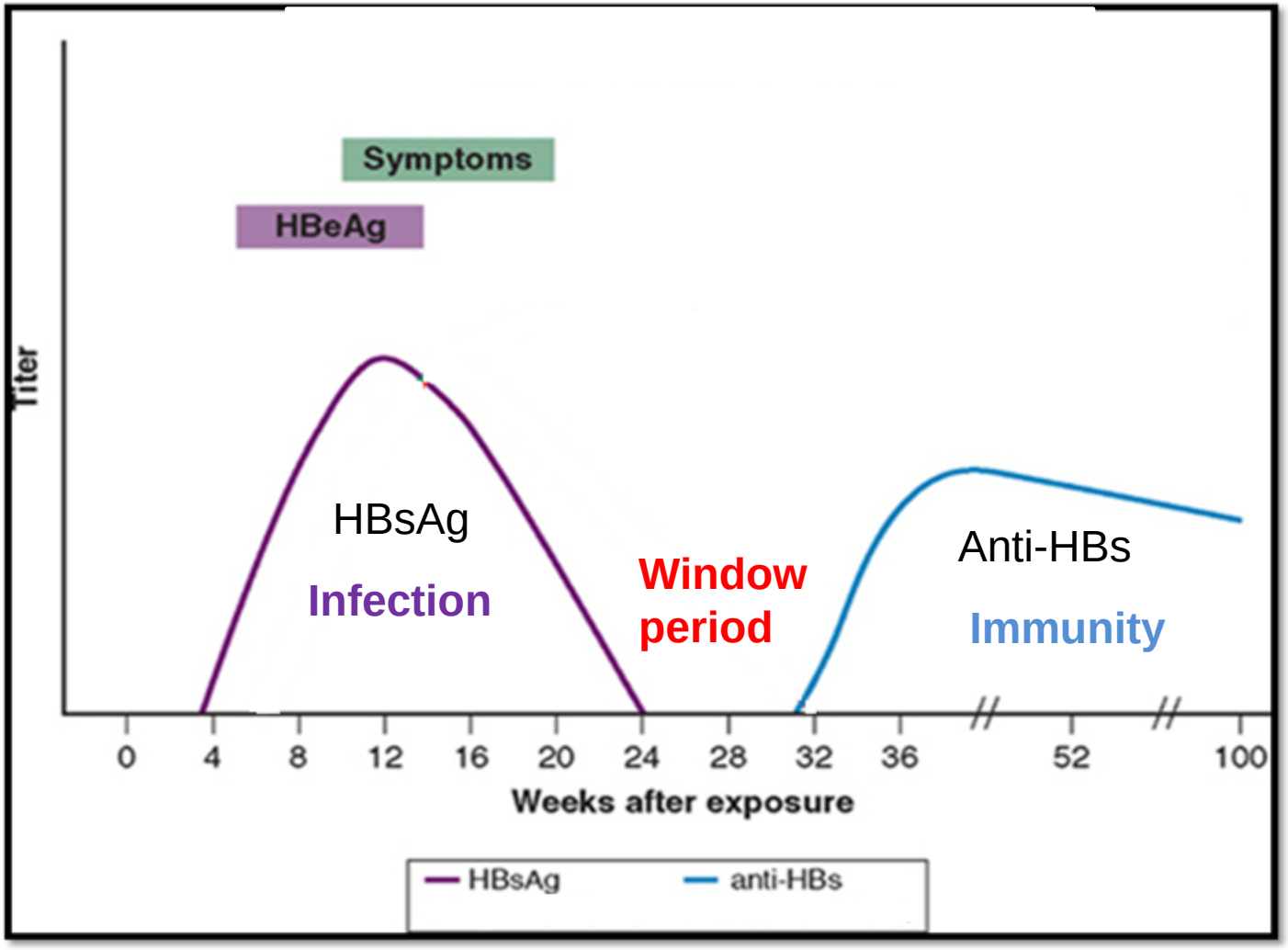
Hepatitis B

- 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**

doesn't mean cirrhosis, thr virus is there but silent, no need to intervene as long as they are stable.

important

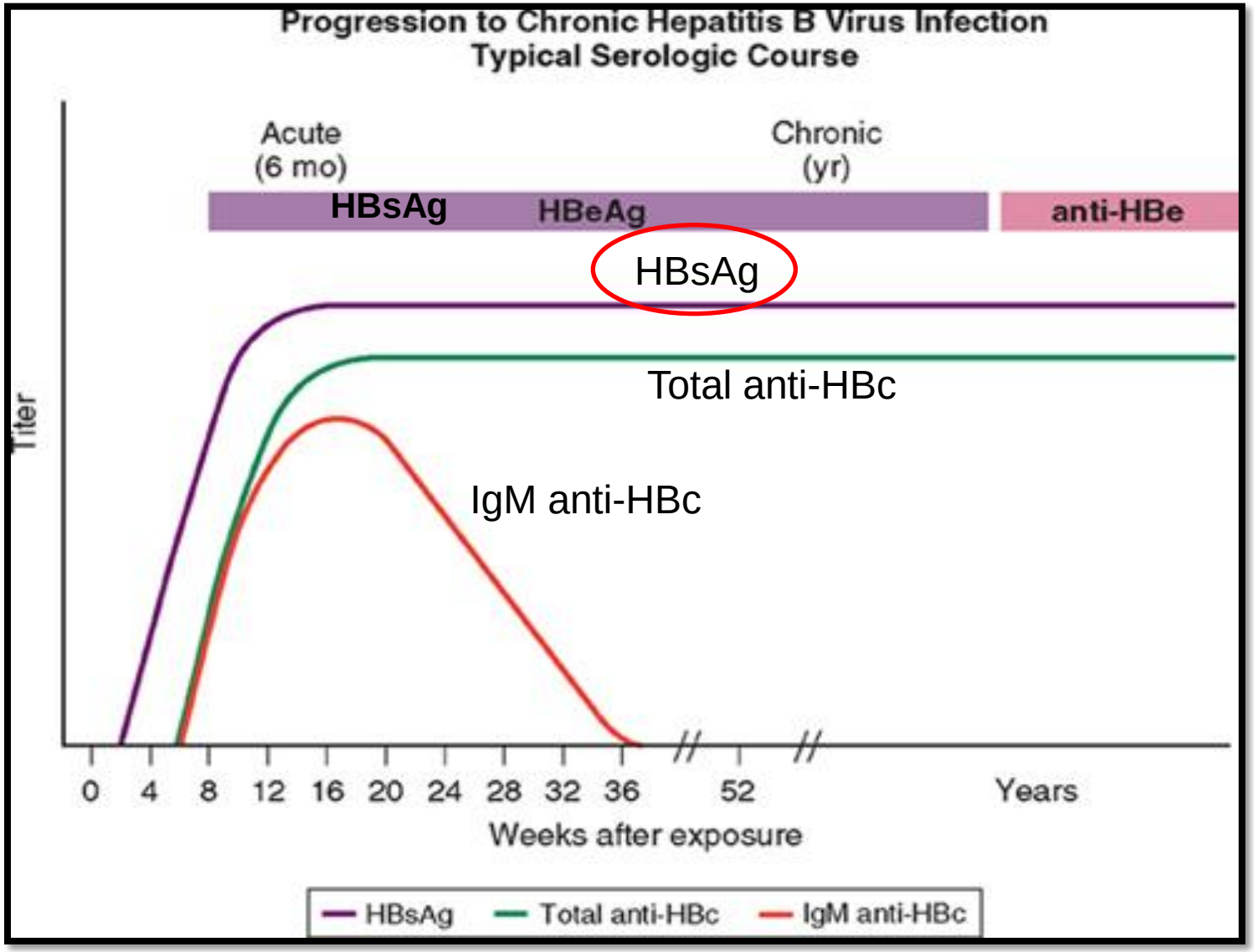
HBV serology markers



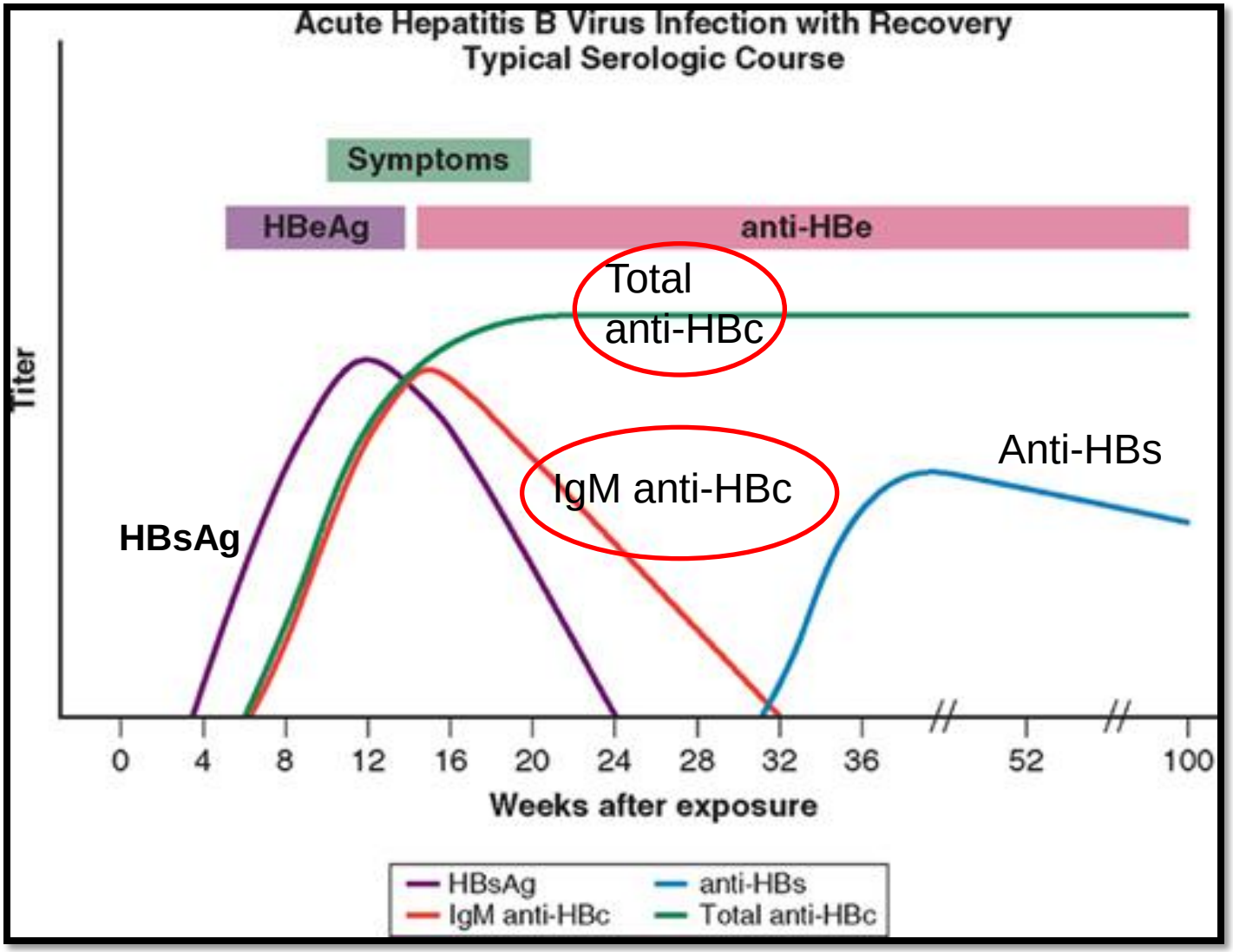
HBsAg and anti-HBs never show up together.

بينما يخرج الأنتجين وقبل ظهور مضاده يكون هناك فترة يغيب فيها كلاهما والتي تسمى window period

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

important:

+ve HBsAg = infection.
+ve HBeAg = infectivity
+ve anti-HBs means immunity, either infection or vaccination, how to differentiate?
if:
+ve anti-HBc = natural infection.
-ve anti-HBc = vaccination.

باختصار الكور تعني أن الڤايرس مر من هنا

Treatment

- **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)

- Older children: antiviral meds

القاعدة أننا لا نستعجل بالعلاج للأطفال
he may recover, or he may live asymptomaic for years,
hep B antiviral meds are toxic and not easy to give.

  - ??? 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 (above 18 ms of age)
  - **confirmed** by PCR for HCV RNA

why after 18 ms? because of maternal ABs

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

- 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

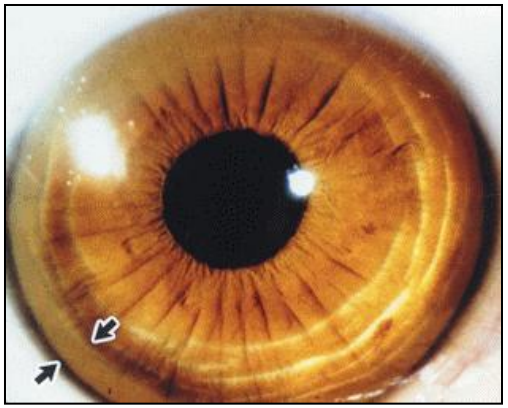
- Hepatitis E virus (HEV) occurs in epidemics in parts of the world that have poor sanitary conditions

- It can be a particularly devastating disease in pregnant women

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 also genetics test, but it takes months

- **Therapy** is **chelating** therapy of the copper with penicillamine, zinc also can be used to treat 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 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