Liver diseases

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 be able to know the most common conditions causing acute & chronic liver diseases in neonates & children & how to diagnose & treat them.

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Special thanks to team 437 & Faisal alsaif

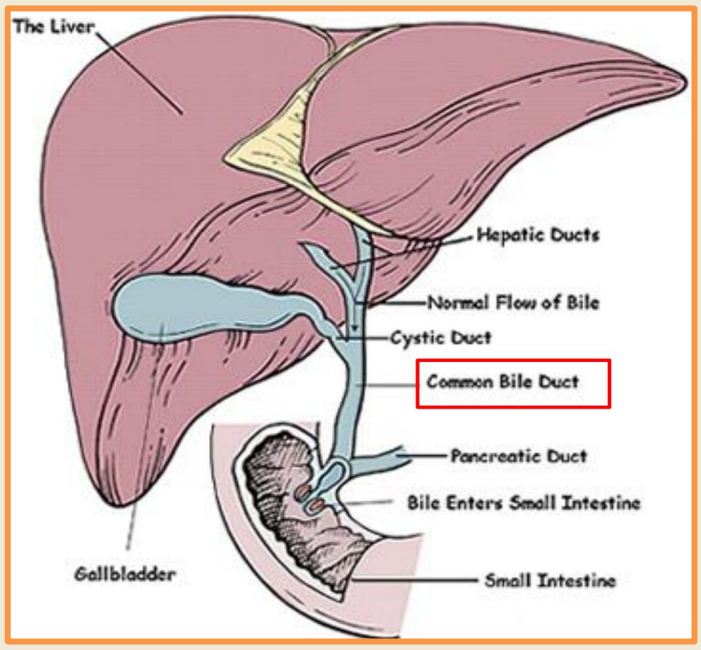
Notes

Important

Book

NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

Liver anatomy:

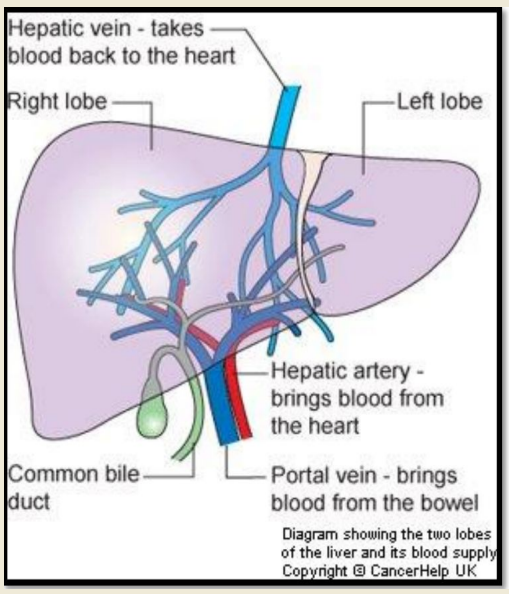


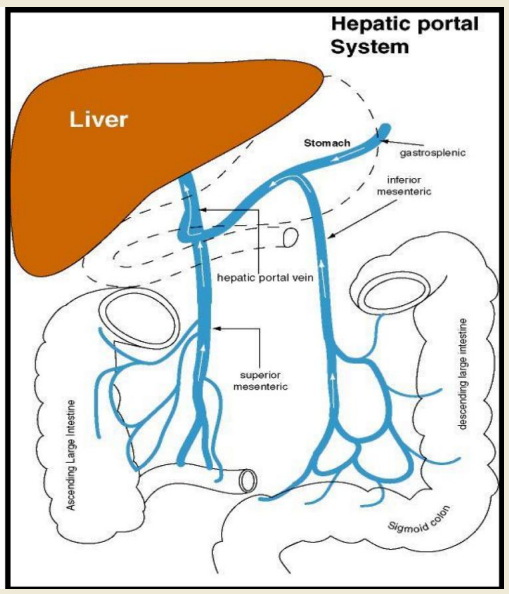
Liver blood supply:

Liver has dual (double) Blood supply resources:

– 70% from portal vein (nutrients) Coming from the viscera

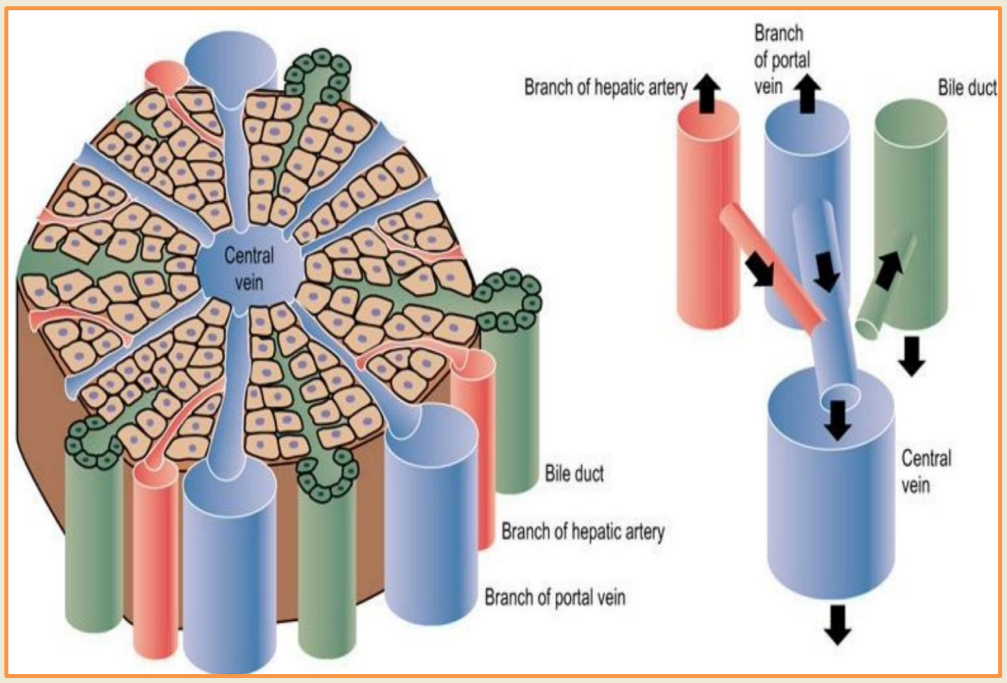
– 30% from Hepatic artery (oxygenated blood)





It's the least organ to be affected in shock. If you find insult caused by shock or hypotension it means the insult is severe.

Liver histology:



We can see here the histological architecture of the liver (it is hexagonal) where we can see:

1. Hepatocytes (all function of the liver happens inside them)
2. Canculi (secretions are excreted here from the hepatocytes), those unite together to form bile ducts

Portal veins are the blue which they form the central vein that descend into the inferior vena cava to the heart

Liver functions

Synthetic Function Very important	• Glucose storage, converts glycogen to glucose in case of fasting. • Plasma proteins: (albumin, globulins, Clotting factors). All protein is from liver. In case of liver disease→edema and malnutrition. • Lipids: cholesterol and lipoproteins. • Bile salts. Important for fat absorption.
Detoxification and excretion	• Bilirubin • Ammonia converted to urea (urea cycle). Excreted in urine. • Drug metabolites • Cholesterol
Storage Function	• Glucose→Glycogen. If high glucose it converts to glycogen • Vitamins A, D, E, K and B12 fat soluble

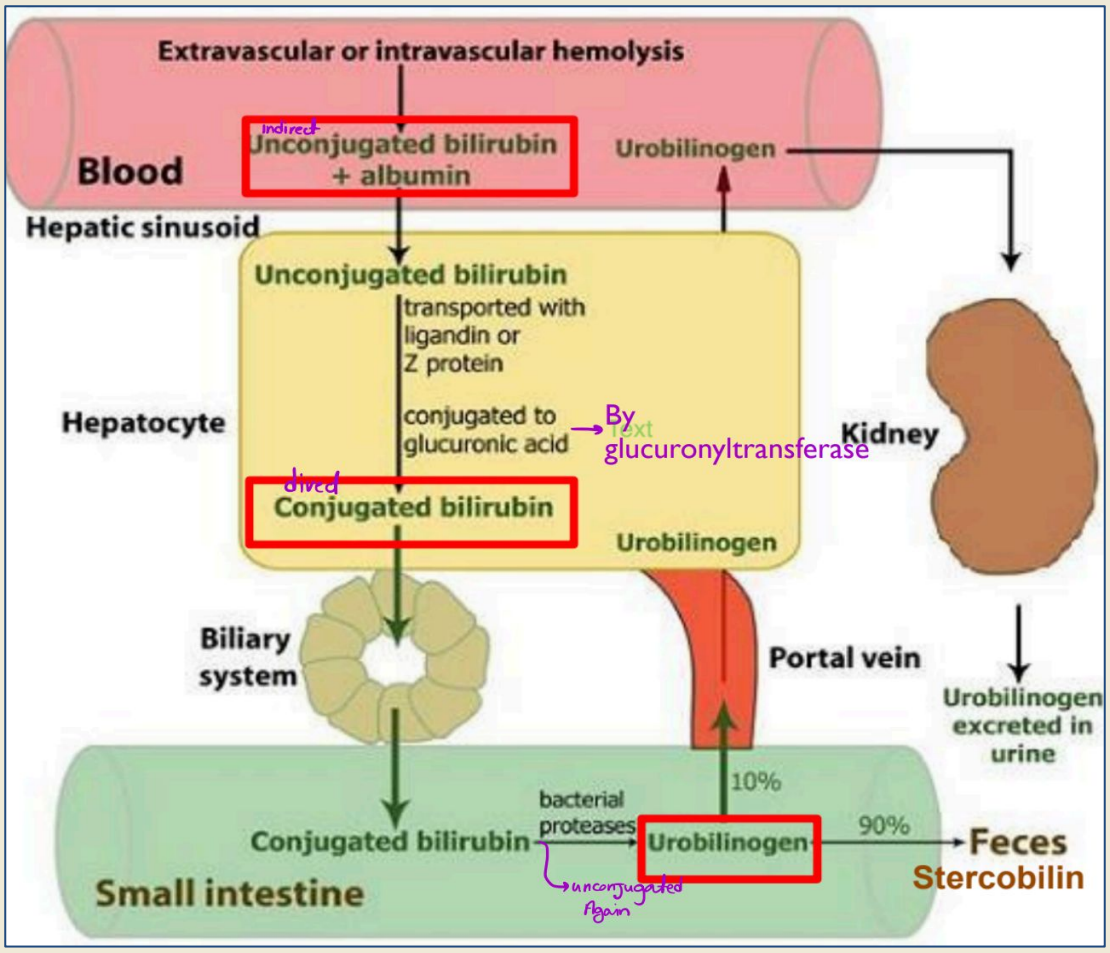
Liver enzymes[1]

Enzymatic markers[2]	**Synthetic function markers** This what tell you if the liver is working or not
• **ALT** (more specific Hepatocellular function) • **AST** (Hepatocellular function) it has different sources such as small bowel, RBCs and muscles diseases • **ALP** (Biliary function) Can come from bones, that's why it's high in growing kids and pregnant women from placenta • **GGT** (more specific for Biliary function)	• **Glucose** • **Bilirubin** • **Bile acids** • **Albumin, Globulins** • **Clotting factors (PT & PTT)** • **Urea (from NH3 & AAs)**

1- In viral hepatitis: LFT are normal but liver enzymes are disturbed. ALT>AST. In gallstones: GGT> ALP

2- when only ALP increases without other enzymes then this tells us that the source of the abnormality is not the liver

Bilirubin metabolism



1- RBCs half-life is about 20 days (life span is 120! Don't confuse it) then it breaks down into different components, one of them is unconjugated bilirubin (fat soluble) it needs to be carried out by albumin inside the blood, then it will be taken to the liver. Inside the liver, it becomes conjugated (water soluble) then it goes to biliary system→ small bowel→ large bowel where it meets normal flora which converts conjugated bilirubin to urobilinogen. 90% of urobilinogen will go through colon and give stool its color. The rest goes to enterohepatic circulation to be reabsorbed and then excreted through the kidney.

2- The clinical importance of this pathway is when we have an obstruction in the biliary system so the bile or bilirubin will not go down to the bowel this will make stool pale or acholic because the bilirubin didn't meet the bacteria inside the colon, thus doesn't give normal color of stool. In pediatrics we think of mechanical obstruction like stone or biliary atresia

Pale stool: metabolic disorder or gallstones..

Hyperbilirubinemia

(important numbers; MCQ)

- **Biochemically = TSB (Total serum bilirubin) > 1.5 mg/dl (26 mmol/l). x17 to convert to mmol.**
- **Jaundice become Clinically evident if total SBL serum bilirubin level > 5 mg/dl (86 mmol/l)**
- **Conjugated Hyperbili(direct):** if Cong. Billi. > 20 % of the total Bili
- **Acute liver failure** = Hepatic dysfunction (hyperbilli & high liver enzymes) + Coagulopathy
  INR >1.5 with encephalopathy
  OR
  INR > 2 without encephalopathy
- **Conjugated(Direct):** HB Liver disease.
- **Unconjugated(Indirect):** HB is mostly non-liver pathology like RBC destruction **EXCEPTIONS** (Indirect hyperbilirubinemia but it's from the liver): Crigler Najjar syndrome and Gilbert syndrome.

Hemolysis	Non-hemolysis
COOMB+ve: • **ABO incompat., Rh incompat** • **Autoimmune** • **Drug-induced HA**	- **Breast feeding/ Breast Milk Jaundice** (most common cause) **How to differentiate?** Breastfeeding jaundice is related to feeding itself occurs in the first few days of life because the mother does not have enough causing dehydration and jaundice. Breast milk jaundice : occurs 1-2 weeks of life. caused by component of the milk that delays conjugation process. Diagnosed by stopping breastfeeding for a few days, bilirubin should decrease. Both benign and mother should continue feeding after that - **Hypothyroidism** Hypothyroidism slow the bowel movement —> more absorbing in the enterohepatic circulation Slow feeder→ dehydration + thyroxine is important for the conjugation process. Can cause ↑ direct bili. - **Crigler Najjar syndrome** - **Gilbert syndrome**
COOMB - ve • **RBC membrane defects** • **Hb pathy** • **Enzyme defects (G6PD)** • **HUS(Hemolytic uremic syndrome)** Physiological jaundice of newborns is common but 90% will have resolved in 2 wks (3 wks if preterm)	

Biochemical Patterns of liver diseases:

1- Isolated Hyperbilirubinemia (HB) (direct vs indirect)
2-Isolated abnormal liver enzymes (w/t HB) (hepatobiliary vs biliary) Very common.
3-Both (Hyperbilirubinemia with abnormal liver enzymes)

They need continuous phototherapy (more than 17hr/day) which can be done in the first few months of life but after that it will be difficult. in very elevated levels they need exchange transfusion & plasmapheresis to remove excess bilirubin from the blood. at the end, the only cure for these kids is liver transplantation although their liver is working fine except for this enzyme. so we don't remove all liver we only do axillary liver transplant (take a small portion of liver from adult donor & connect it to patient's liver)

Isolated Hyperbilirubinemia

	Disease	Defect	Manifestations	TREATMENT
Indirect	**Gilbert's syndrome** Present at childhood - adolescent	**Mutation in UGT1A1** (< 30% of the normal activity) of the enzyme UGT1A1	Mild jaundice during **stress** Fasting, sick	None
Indirect	**Crigler-Najjar syndrome type 1** In infants	**Mutation in UGT1A1** (absent activity) → No glucuronyltransferase	**Sever** jaundice (risk for **kernicterus**) Permanent CNS insult If not treated early	PhtoTx for 17h/d; Exchange Tf (Transfusion) → Early Tx; Liver Tp → Definitive therapy
Indirect	**Crigler-Najjar syndrome type 2** In infants Milder form	**Mutation in UGT1A1** (< 10% of the normal activity)	Mild-mod jaundice	Phonoparbitone This will induce enzyme activity → No need for liver Transplant
	Direct HB Both benign, present after delivery			
	Dubin-Johnson syndrome	MRP2 receptor mutation (impair **transport** process across canalicular membrane)	Neonatal cholestasis – no symptoms	None → Resolve in adulthood (benign)
	Rotor syndrome	OTP1B1 & OTP1B3 mutation (affect **reuptake** of cong.Billi by hepatocytes)	Neonatal cholestasis – no symptoms	None → Resolve in adulthood (benign)

gilbert syndrome manifest as mild jaundice during stress such as fasting

Pattern of liver enzymes:

- **Cholestatic or obstructive bile duct injury**
  a.**GGT /ALP** > AST/ALT
- **Hepatocellular or liver cell injury:**
  a.**ALT/AST** > GGT/ALP
- **Mixed: Mostly ratio is what matters**

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

Liver disease in children

- **Variable liver disease in children (age dependent):**

  - Infants: (congenital/metabolic/genetic disorders):
  -Biliary atresia (BA), only comes after 2 weeks of birth
  -Neonatal hepatitis, metabolic liver disease and genetics disorders
  -Familial intrahepatic cholestasis(PFIC)

  -Older children = adults liver diseases:
  Viral Hepatitis, Wilson disease, Autoimmune hepatitis, ect…

- **The main presenting symptoms of liver disease is jaundice** but can be incidental

- **Any jaundice after 2 weeks of age should be investigated. First two week high levels are normal.(MCQ)** More than 3 weeks in preterm

Cholestatic liver disease

Cholestasis ➡ chole= bile Stasis=stagnation

- **The obstruction of bile flow either:**

  -Mechanical block (biliary atresia, stones…)
  -Functional block (cellular receptor & transporter levels): e.g progressive familial intrahepatic cholestasis (PFIC), sepsis, TORCH On U/S it's normal, More seen in infections, genetic/metabolic disorders, hypothyroidism.

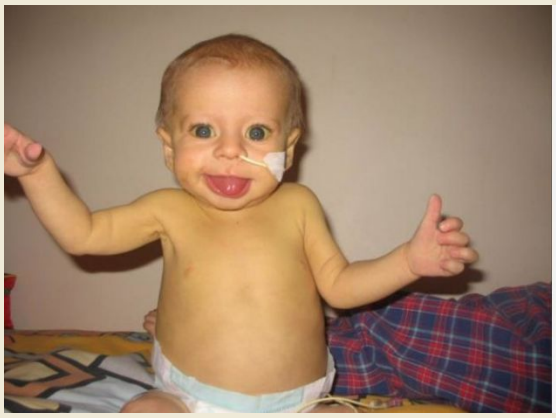
- **Cholestasis is characterized by an accumulation of compounds that cannot be excreted through the bile**

  - Conjugated / direct bilirubin => jaundice
  - Enzymes (GGT/ALP>ALT/AST) => high liver enzymes in serum
  - Bile acids => itching it deposits under the skin. It could be severe enough to indicate liver transplant.
  - Cholesterol => xanthomas

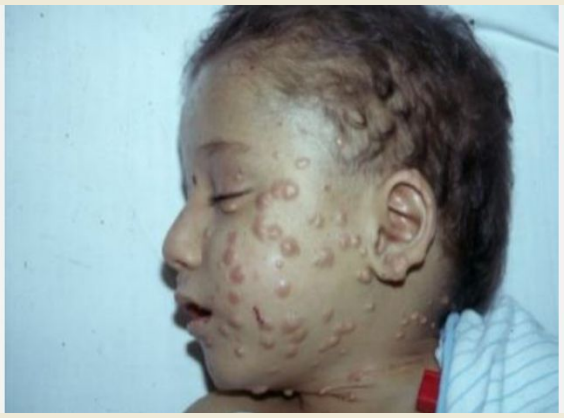
- **Presentation of cholestasis:**

Jaundice (accumulation of conjugated bilirubin)
Pale stool (Acholic stool)… Why? (MCQ) Obstruction→bilirubin won't reach normal flora in colon→won't form urobilinogen→ pale stool
Dark and foamy urine (bile salts in the urine)+ bilirubin.
Pruritus (accumulation of bile acids under the skin)
Xanthomas depositions (accumulation of cholesterol in the skin)
Hepatomegaly +/- Splenomegaly (Portal HTN, Storage disease, infiltrative process)
Failure to thrive (FTT)very common in chronic liver disease**/ poor weight gain**
Incidental lab finding

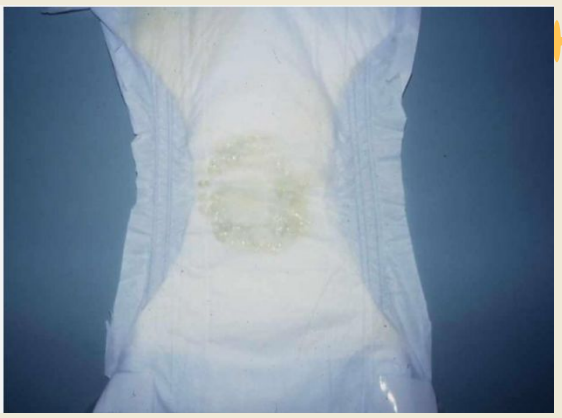
Signs of cholestatic liver disease



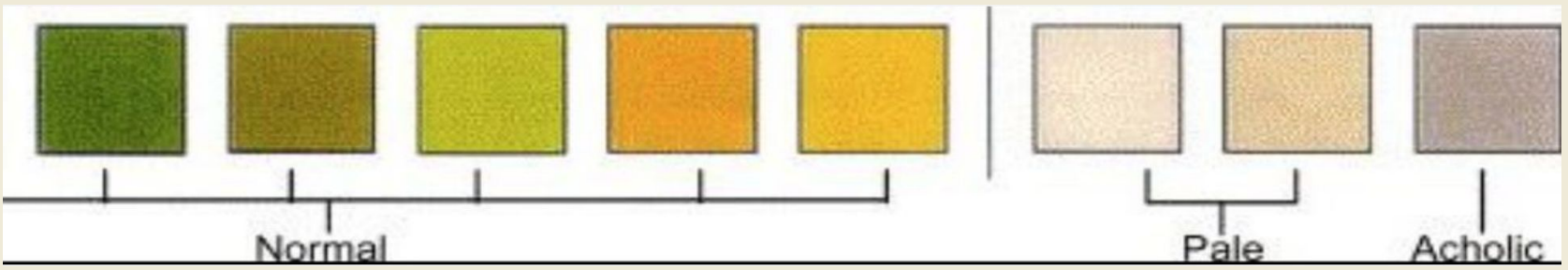
Jaundice+abdominal distention(ascites) +muscle wasting + failure to thrive> need NGT feeding



Xanthomas- (alagille syndrome). Resolves with transplant and doesn't affect CVS.



Pale stool (acholic stool) dangerous.



This is a stool card, given to parents in countries where cholestatic liver disease is common (east asia) to bring baby if abnormal color. Early diagnosis> avoid irreversible liver damage.

Evaluation of infants with cholestatic liver disease

STEP1: Confirm the presence of cholestasis Clinically: jaundice, acholic stool, pruritus, & lab: direct hyperbili) high GGT

STEP 2: Rule out surgical obstruction such as Biliary atresia, Choledocal cyst and GB stones **(imaging studies eg. Abdm US)** if normal go to step 3

STEP 3: Investigate the treatable medical conditions:

- **Infections:** UTI, TORCH infections bacteria secretes toxins that affects conjugation process, easy to treat with antiviral/antibacterial therapy.
- **Endocrine:** hypothyroidism, panhypopituitarism
- **Metabolic disorders** (Galactosemia, Tyrosinemia)

STEP 4: Further studies for other causes (genetic/metabolic)

Hepatocellular liver disease

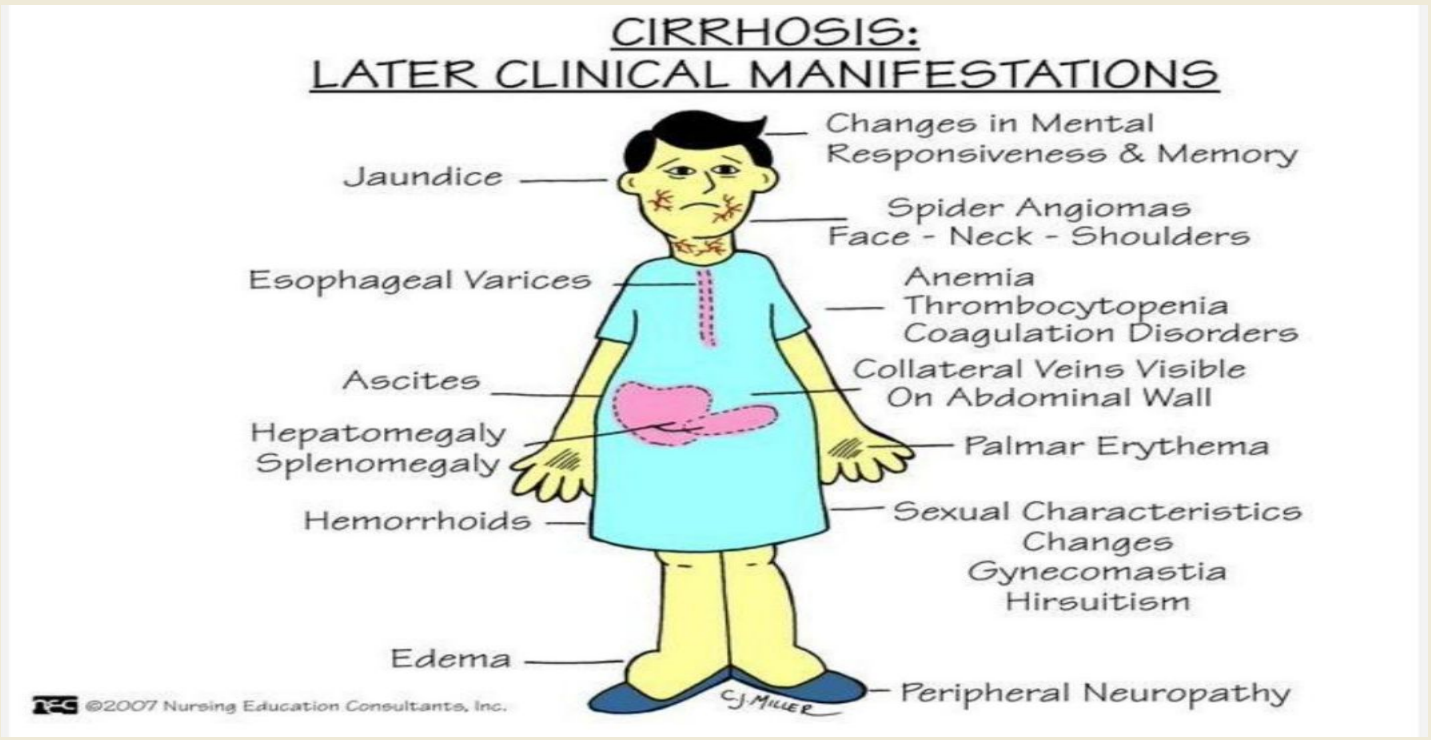
- **Necrosis of hepatocytes** following a **viral, ischemic or toxic insult or herbal** to the liver will cause primarily an elevation of enzymes found within the hepatocyte **(ALT and AST)**
- **In hepatocellular disease, ALT/AST>>GGT/ALp (in general) (GGT and ALP do NOT rise in the same degree as ALT and AST)**

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.** But not necessary cirrhosis

- **Chronic hepatitis in children can be caused by:**
  -viral infection (Hep B & C); autoimmune process; hepatotoxic drugs; or metabolic, or systemic disorders e.g leukemia and lymphoma

- **Can progress to Chronic liver disease if the primary disease not treated well**
- Acute hepatitis→chronic hepatitis→cirrhosis (irreversible)(when hepatocytes become fibrous and non-functioning.)



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

Doctor said you need to go through the red

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' hemoltic 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

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)

SPECIFIC LIVER DISEASES IN INFANTS

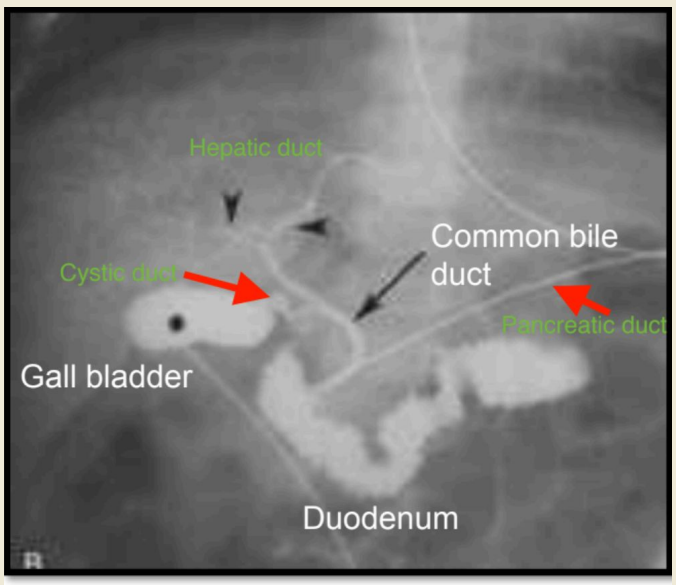
MCQ IMP

Biliary Atresia (BA)

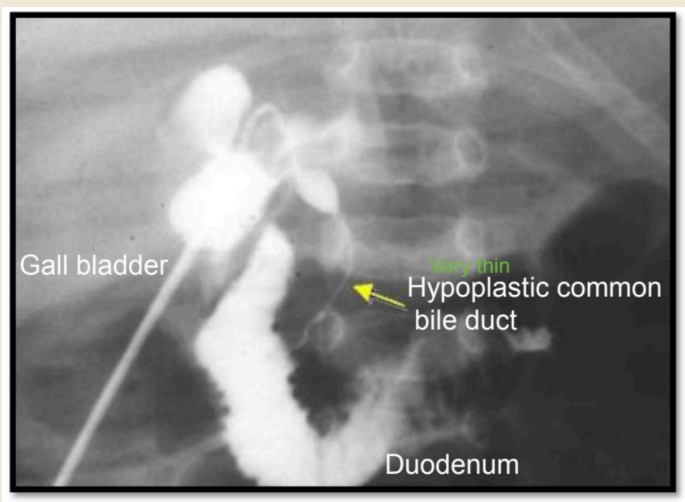
- **Biliary atresia is an obstructive disease of the biliary tree (mainly extra-hepatic) secondary to idiopathic inflammatory/autoimmune process??** The theory is it's caused by intrauterine viral infection (CMV)
- **It leads to gradual fibrosis and ultimate obliteration of the biliary tract -> biliary cirrhosis(I**F INFLAMMATION REACHED THE LIVER)**-> liver failure -> infant death within 2 years If not treated (surgery or liver transplantation)**
- **The most frequent indication worldwide for liver transplantation among infants and children (NOT in KSA)** In KSA metabolic and genetic disorders are more common and most common is progressive familial intrahepatic cholestasis (PFIC) but in exam choose atresia

BA Diagnosis: We rarely order ERCP in young peds

- **Clinical presentation: It presents with signs of cholestasis** (jaundice, acholic stool, pruritus, FTT) **in the first 2-6 weeks of life (MCQ)** Thus, if the baby is < 2wks w/ jaundice, it's NOT biliary atresia
- **Abdominal US: rule out other causes of biliary obstruction** (choledochal cyst congenital anomaly that affects biliary system, GALLstones. Shows contracted or absent gallbladder
- **Hepatobiliary scintigraphy = nuclear scan (HIDA scan): shows good uptake of tracer and then NO excretion into the intestine, even 24 hours later.** We do it if pt presents early, needs long time to prepare, if late do biopsy
- **liver biopsy**
- **Definitive diagnosis is confirmed by Intraoperative cholangiogram** If normal, take liver biopsy to look for other causes. It is done by The surgeon inserts a catheter inside the gallbladder through the skin, injects a dye that goes from GB →cystic duct→biliary system (clear hepatic, common biliary, and pancreatic duct) → small bowel. This is the normal pathway



Normal study

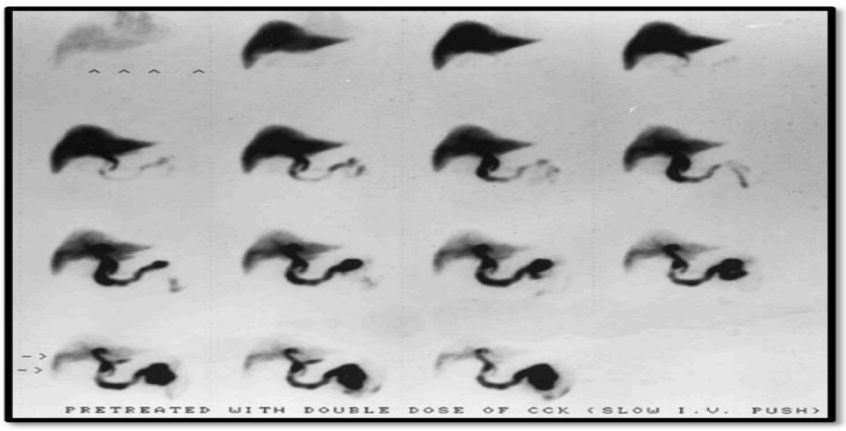


Abnormal study (hypoplastic common bile duct)

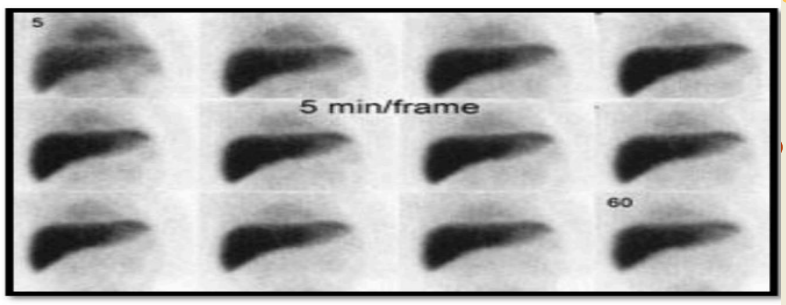
This confirm the diagnosis > take child directly to the OR > Kasai procedure

Hepato-biliary scintigraphy (HIDA scan)

Ddx of biliary atresia



NORMAL HIDA SCAN



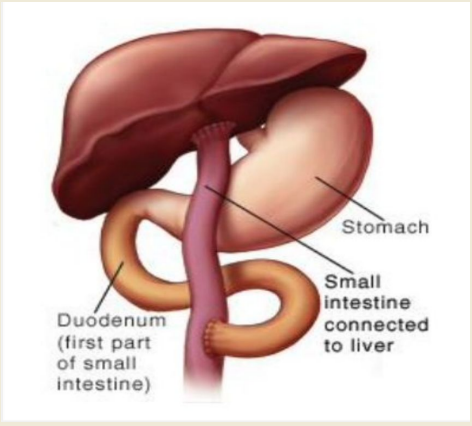
HIDA scan in BA patient

- **BA Management:**

-Surgical correction (Kasai procedure or portoenterostomy) : also called hepato-entero-stomy and it is done by removing the blocked bile ducts and gallbladder and replacing them with a segment of child own intestine.

-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) the earlier the better the outcome

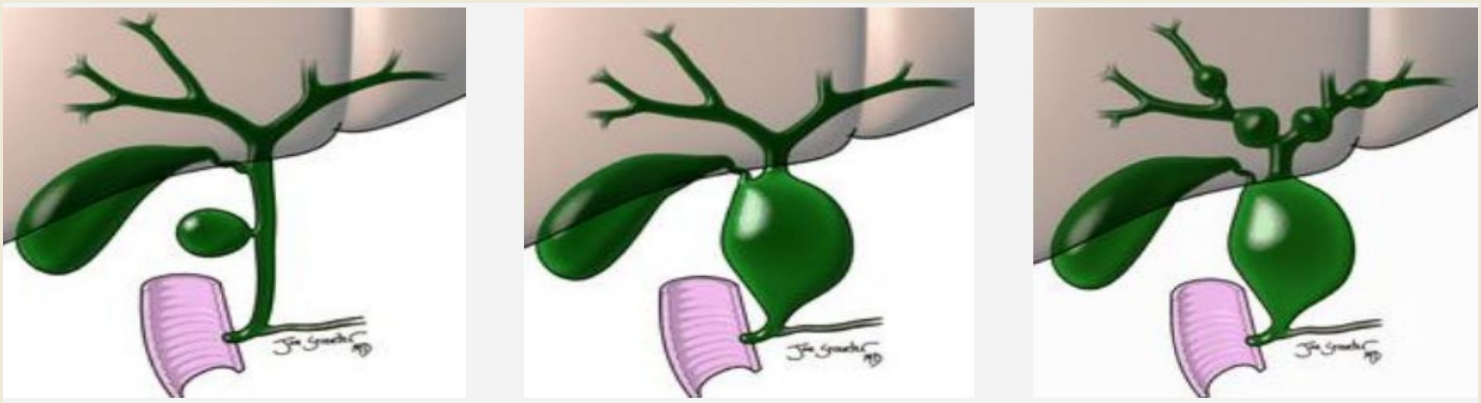
- Liver transplantation if:
1-Kasai failed
2-Late presentation (> 3 months)
3-Decompensated liver disease



Choledocal cyst

Ddx of biliary atresia

- **Cystic dilatation of the biliary tree at different levels ->obstructive picture** Very common. diagnosed with US or MRA
- **Present same as BA with cholestasis picture, abdominal mass or asymptomatic, biliary stones or biliary carcinoma in adults.**
- **Treatment: surgical excision** With the formation of Roux-en-Y anastomosis to the biliary duct



Only resect cyst Have to resect the whole section

Alpha-1 Antitrypsin deficiency

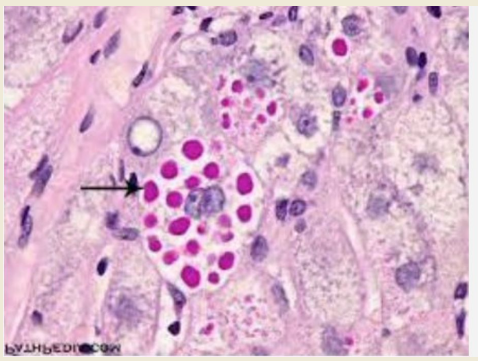
- **Elastase and trypsin are released from the body when lung cells are destroyed, when there's a deficiency of antitrypsin this causes destruction of the lung and emphysema. In the liver the issue is accumulation of Pi ZZ.**

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

- **A-1 AT deficiency cause 2 forms of diseases:**
  1-Liver disease (children or adults)
  2-Emphysema lung disease (mainly seen in adults) Advice to avoid smoking

- **AR disease(Autosomal recessive) rare in our community**
- **Pi MM (normal) -> Pi ZZ (diseased) -> form abnormal A-1 AT protein -> failed excretion from liver (trapped) -> cholestatic liver disease.**

- **DX:**
  -A-1 AT level, phenotyping (pi ZZ) instead of normal pi MM
  -confirmed with Liver biopsy (seen in special stain)
  -Genetics



- **Treatment: supportive**

- **Prognosis: variable (improve over time -> chronic liver disease**

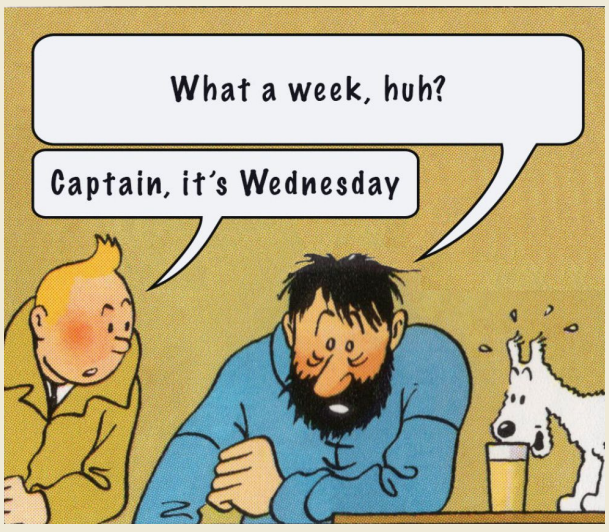
Neonatal Hepatitis

Condition that doesn't have specific diagnose, old term

- **"Idiopathic" neonatal hepatitis (NH) =** an aetiology has not been identified

- **The list of NH is getting smaller overtime** (bcz. of new advancement in diagnostic modalities = more genetic & metabolic causes are discovered daily)

- **Management of these infants involves supportive measures till specific cause found**



Take a break and watch this!

Click here

SPECIFIC LIVER DISEASES IN OLDER CHILDREN

Liver disease in older children = adults !!

Causes high ALT/AST

- **Infectious (Viral, Bacterial, Protozoal)**
- **Toxic/medications (drugs, TPN)**
- **Ischemia (CR arrest, hypotension)**
- **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 -> (hepatocellular injury -> mixed)**

HEPATITIS A: (MCQs)

The most common

- **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)** Shouldn't go to school for 2 weeks.

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

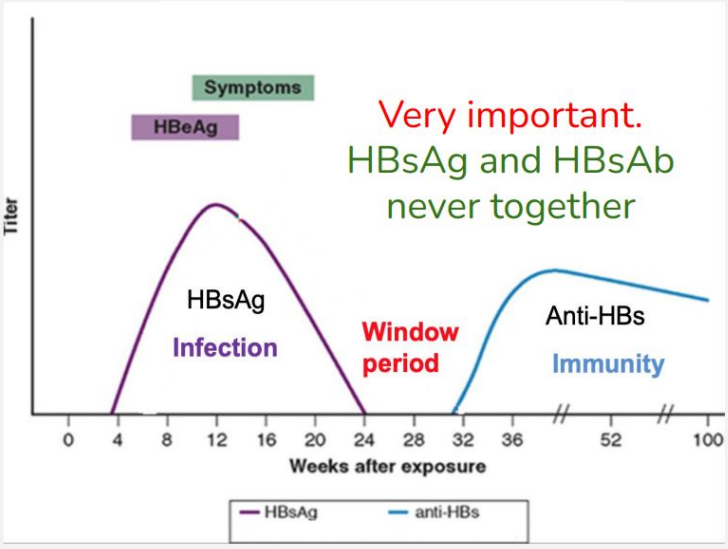
- **Diagnosis s of acute infection is based on the presence of anti-HAV IgM antibody in serum (MCQ)** And markedly elevated transaminase, coagulation is usually normal.

- **The disease typically is self-limited in children and often is clinically not clear,** In very rare cases, fulminant hepatic failure with severe necrosis of hepatocyte occurs and needs liver transplant.

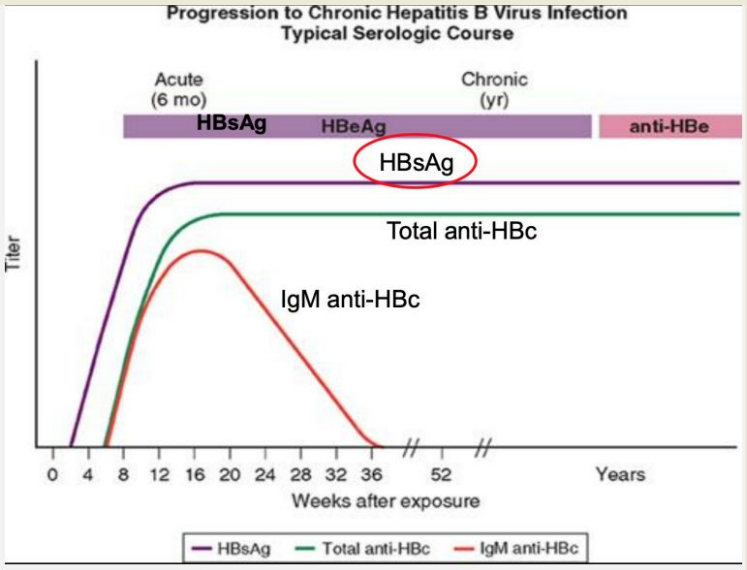
- **No chronic carrier state is identified** (full recovery or rarely death from fulminant liver failure)
- **Treatment** is supportive (IVF, Antipyretics)
- **Prevention:** Hep. A vaccine: 2 doses (18 ms & 24 months

Hepatitis B

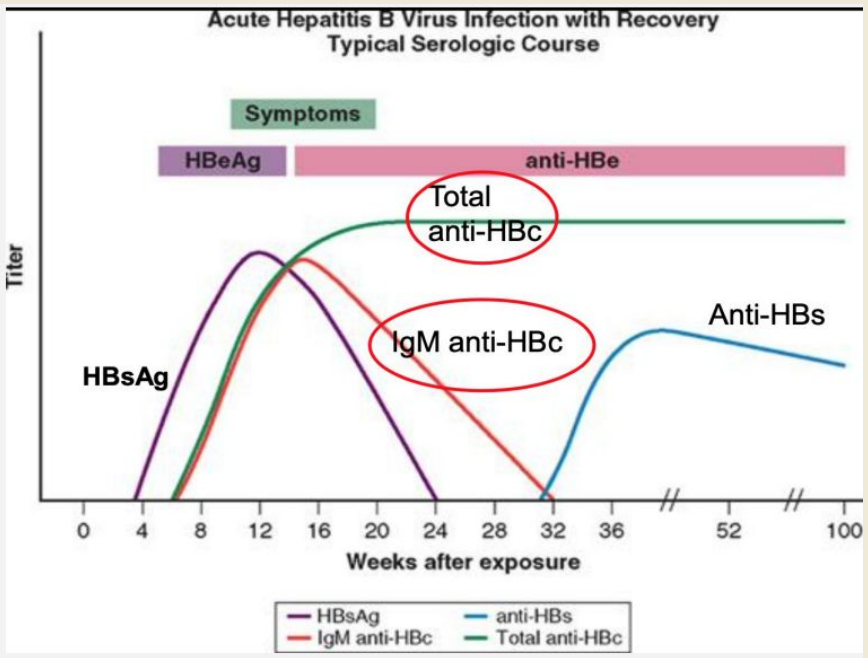
- **Hepatitis B virus (HBV) infection can cause both <u>acute and chronic hepatitis</u>**
- **It can progress to cause cirrhosis and hepatocellular carcinoma if not treated (take long time to happen)** **A**ny cirrhosis can lead to cancer. HBV can also cause HCC without progressing into cirrhosis!!!!
- **Risk of transmission:** primarily vertical (mother to baby during delivery) in children or via contaminated blood + other risk factors. In adult, sexually
- **Diagnosis:** Hepatitis B surface antigen **(HBsAg)**
- **<u>Chronic HBV infection is associated with the persistence of HBsAg and HBV DNA for > 6 months</u>**



HBV serology markers



Chronic hepatitis



HBV serology markers..
recovery

Hepatitis B

Hepatitis B serological markers

Never the same antigen and antibody presents together

Imp to your future, USMLE.. etc

* HBsAg => Hepatitis B surface antigen

* Anti-HBs => Hepatitis B surface antibody

* Anti-HBc => hepatitis B core antibody

* IgM Anti-HBc => IgM antibody to hepatitis B core antigen

* HBeAg => Hepatitis B e antigen

* HBeAb => Hepatitis B e antibody

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

HBsAg => +ve => Infection
If it was:
IgM Anti-HBc => acute infection
IgG Anti-HBc => chronic infection

Anti-HBs => +ve => Immunity

How to differentiate when Anti-HBs is +ve whither it's previous infection or got vaccinated? (both have -ve HBsAG & +ve Anti-HBs)

By Anti-HBc
Vaccinated => -ve Anti HBc
Infected (natural immunity) => +ve Anti-HBc

HBeAG => +ve => high infectivity
HBeAb => +ve => low infectivity

- **Treatment:**

-Prevention: more imp than treatment.

-Newborn of Hep BsAg-positive mothers (MCQ): Prevent >95% of infections

- **PASSIVE immunization: Hep. B Immunoglobulins (within 12 hrs of birth)**
- **ACTIVE immunization: Hep. B Vaccine after birth (within 7 days after birth, then at 1 month & 6 months)**

-Rx for older children: if the liver enzymes were normal we don't do anything, we give the medication when the body immune system starts attacking the virus and ALT/AST is high

-Wait & observe (spontaneous recovery, new better antiviral meds with less side effects)

Hepatitis C

- Hepatitis C virus (HCV) causes acute hepatitis, **which progresses to chronic disease (End-stage liver disease can occur in up to 10 %)**
- Risk of transmission similar to hepatitis B

Diagnosis: is based on the detection of

- persistently elevated **anti-HCV antibodies (AFTER 18 ms of age: why?)** because below 18 month we will find the mothers anti-hcv antibodies in the baby's blood but if we find it after 18 month then it's for sure the baby's antibodies
- **anti-HCV indicates the presence of the virus (**exposure**) but tell nothing about its activity or the immunity status.** Liver enzymes tell us about its activity.
- **Confirmed by PCR for HCV RNA-active infection**

Treatment:

- **Spontaneous viral clearance from acute infections can occur in pediatrics (15-56%)**
- **antiviral Rx** (new generation, > 95% effective) start immediately Always give treatment (vs. Hep B we wait)
- **Prophylaxis:** no vaccine yet

Hepatitis D

- Hepatitis D virus (HDV) infection occurs only in patients who have HBV infection esp if severe,Co-infection with hep B or superinfection causing acute exacerbation of chronic hep B infection
- Associated primarily with **intravenous drug abuse**
- HDV usually aggravates liver disease in a patient who has hepatitis B and always should be considered in those who have particularly aggressive HBV disease

Hepatitis E

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

Viral hepatitis.. summary

	Hepatitis A virus (HAV)	Hepatitis B virus (HBV)	Hepatitis C virus (HCV)	Hepatitis D virus (HDV)	Hepatitis E virus (HEV)
Viral genome	RNA	DNA	RNA	RNA	RNA
Transmission	Fecal-oral route	Blood and other body fluids	Blood	Blood and other body fluids	Fecal-oral route
Incubation period	14-28 days	30-180 days	14 days - 6 months	HDV requires HBV for replication	14-70 days
Diagnosis	- anti-HAV specific AB - HAV RNA	- HBV surface protein - anti-HBV specific AB	- anti-HCV specific AB - HCV RNA	- anti-HDV specific AB - HDV RNA	- anti-HEV specific AB - HEV RNA
Possible chronic infection	No	Yes	Yes	Yes	Yes
Vaccine	Yes	Yes	No	No	Yes (in china only)

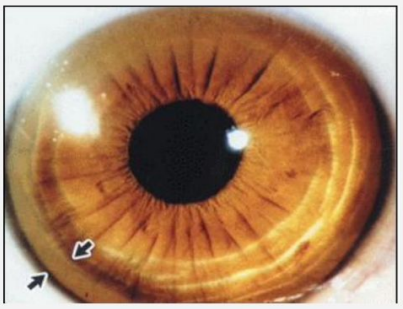
Wilson disease

Very very imp

One of the few treatable genetic disorders

- **AR disorder**

- **Caused by a defect in biliary copper excretion**
  And decrease synthesis of **ceruloplasmin** (copper binding protein)



Copper accumulation in the cornea (Kayser–Fleischer rings) is not seen before 7 years of age.

- **Excessive copper accumulation (multi-systems):**

  -Liver -> leads to cholestasis -> cirrhosis
  -Other organs: cornea(cloudiness), kidneys (nephropathy), and brain(psychosis and depression), hypothyroidism, cataract, resulting in extrahepatic manifestations of the disease. Vitamin D resistant rickets

- 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. Take pt to ICU

- Wilson disease SHOULD BE INCLUDED in the differential diagnosis of any child above 5 yrs of age who presents WITH:

  -Liver disease
  -Neurologic abnormalities
  -Behavioural changes if > 5 years, that's why it's important to exclude it.

- Treatable condition if less 5 years because they did not reach sx phase.

- **Definitive diagnosis** requires evaluation of:
  -24-hour urinary copper excretion
  -copper quantification in liver tissue obtained by biopsy
  -**Genetic test** (useful in asymptomatic children of 1st degree relatives)

- Therapy is chelating therapy of the copper with penicillamine, which allows for copper excretion into the urine. Binds to copper.Zinc is given to reduce the copper absorption and pyridoxine to prevent peripheral neuropathy

- Early diagnosis = better prognosis If not treated> cirrhosis

AIH(Autoimmune hepatitis) 438 slides

- 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 438 slides

- Ischemic hepatitis results from **shock (eg, dehydration), asphyxia,**

- **cardiorespiratory arrest, or seizures.**

- The disorder is due to hypotension/hypoperfusion to the liver

- **Typically, amino transaminases 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 amino transaminases levels in the days following the initial insult without increasing coagulopathy or hyperbilirubinemia.

Infiltrative disorders 438 slides

- Infiltrative disorders of the liver are observed with leukemia, lymphoma, and neuroblastoma (more common than primary liver tumors)

- Primary liver tumors: Hepatoblastoma, hepatocarcinoma, and hemangioendothelioma

- Presentation: hepatomegaly or abdominal distension or mass

- Serum alpha-fetoprotein levels usually are elevated.

- Dx by CT scan or MRI

- Surgical excision of a solitary tumor or radiation/chemotherapy is the treatment of choice.

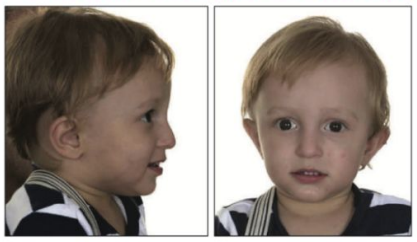
TABLE 6. Miscellaneous Physical Findings Associated With Liver Disease

Infants	Children
• Microcephaly: congenital cytomegalovirus, rubella, toxoplasmosis	• Pruritus: chronic cholestasis
• Characteristic facies: arteriohepatic dysplasia (Alagille syndrome)	• Hemangiomas: hemangiomatosis of the liver
• Cataracts: galactosemia	• Kayser-Fleischer rings: Wilson disease
• Retinal pigmentation and posterior embryotoxon: Alagille syndrome	• Glossitis: cirrhosis
• Abnormal auscultation of lungs: cystic fibrosis	• Enlarged kidneys: congenital hepatic fibrosis or polycystic disease
• Neuromuscular abnormalities (tremors, flaccidity): lipid storage disease, Wilson disease, disorders of oxidative	• Arthritis and erythema nodosum: liver disease with chronic inflammatory bowel disease
	• Arthritis, acne, fatigue: autoimmune hepatitis

Extra

Alagille syndrome:

This is a rare autosomal dominant condition with widely varying penetrance even within families.
Clinical presentation is with a characteristic triangular facies, skeletal abnormalities (including butterfly vertebrae), congenital heart disease (classically peripheral pulmonary stenosis), renal tubular disorders, and defects in the eye. Infants may be profoundly cholestatic with severe pruritus and faltering growth.
Identifying the gene mutations confirms the diagnosis.
Treatment is to provide nutrition and fat-soluble vitamins. Pruritus is profound and difficult to manage. A small number will require liver transplant, but most survive into adult life. Mortality is most likely secondary to the cardiac disease.



(a) (b)

Figure 21.4 The typical facial features of a child with Alagille syndrome with (**a**) pointed chin and (**b**) wide spaced eyes and prominent forehead.

Progressive familial intrahepatic cholestasis:

These autosomal recessive disorders all affect bile salt transport.
Clinical presentation is with jaundice, intense pruritus, faltering growth, rickets, and in some cases diarrhoea and hearing loss.
Older children may present with gallstones.
The diagnosis is confirmed by identifying mutations in bile salt transport genes.
Treatment is with nutritional support and fat-soluble vitamins. Pruritus can be severe. Progression of fibrosis is usual with most requiring liver transplantation.

Acute liver failure in children is the development of massive hepatic necrosis with subsequent loss of liver function, with or without hepatic encephalopathy.
The disease is uncommon, but has a high mortality. The child may present within hours or weeks with jaundice, encephalopathy, coagulopathy, hypoglycemia, and electrolyte disturbance.
Early signs of encephalopathy include alternate periods of irritability and confusion with drowsiness. Older children may be aggressive and unusually difficult.

Complications: cerebral edema, haemorrhage from gastritis or coagulopathy, sepsis and pancreatitis.

Diagnosis: Bilirubin may be normal in the early stages, particularly with metabolic disease. Transaminases are greatly elevated (10–100 times normal), alkaline phosphatase is increased, coagulation is very abnormal and plasma ammonia is elevated.
It is essential to monitor the acid– base balance, blood glucose and coagulation times.
An EEG will show acute hepatic encephalopathy and a CT scan may demonstrate cerebral oedema.

Management: Early referral to a national paediatric liver centre is essential.
Steps to stabilize the child prior to transfer include:

- maintaining the blood glucose (>4 mmol/L) with intravenous dextrose
- preventing sepsis with broad-spectrum antibiotics and antifungal agents
- preventing haemorrhage, particularly from the gastrointestinal tract, with intravenous vitamin K and H2-blocking drugs or PPI
- prevent cerebral edema by fluid restriction and mannitol diuresis if edema develops.

Features suggestive of a poor prognosis are a shrinking liver, rising bilirubin with falling transaminases, a worsening coagulopathy, or progression to coma.
Without liver transplantation, 70% of children who progress to coma will die.

Table 21.1 Causes of acute liver failure

Children <2 years old	Children >2 years
Infection (most common is herpes simplex)	Seronegative hepatitis
Metabolic disease	Paracetamol overdose
Seronegative hepatitis	Mitochondrial disease
Drug induced	Wilson disease
Neonatal haemochromatosis	Autoimmune hepatitis

Autoimmune hepatitis and sclerosing cholangitis:

- The mean age of presentation is 7 years to 10 years. It is more common in girls.
- It may present as an acute hepatitis, as fulminant hepatic failure or chronic liver disease with autoimmune features such as skin rash, arthritis, haemolytic anaemia, or nephritis.
- Diagnosis is based on elevated total protein, hypergammaglobulinaemia (IgG >20 g/L); positive autoantibodies, a low serum complement (C4); and typical histology.
- Autoimmune hepatitis may occur in isolation or in association with inflammatory bowel disease, coeliac disease, or other autoimmune diseases.
- Some 90% of children with autoimmune hepatitis will respond to prednisolone and azathioprine. Scerosing cholangitis is treated with ursodeoxycholic acid.

Cystic fibrosis

- Liver disease is the second most common cause of death after respiratory disease in cystic fibrosis.
- The most common liver abnormality is hepatic steatosis (fatty liver). It may be associated with protein energy malnutrition or micronutrient deficiencies. Steatosis does not generally progress and treatment involves ensuring optimal nutritional support. More significant liver disease arises from thick tenacious bile with abnormal bile acid concentration leading to progressive biliary fibrosis.
- Early liver disease is difficult to detect by biochemistry, ultrasound or radioisotope scanning. Liver histology includes fatty liver, focal biliary fibrosis, or focal nodular cirrhosis.
- Supportive therapy includes endoscopic treatment of varices and nutritional therapy and treatment with ursodeoxycholic acid.
- Liver transplantation may be considered for those with end-stage liver disease, either alone or in combination with a heart–lung transplant.

Fibropolycystic liver disease (ciliopathies):

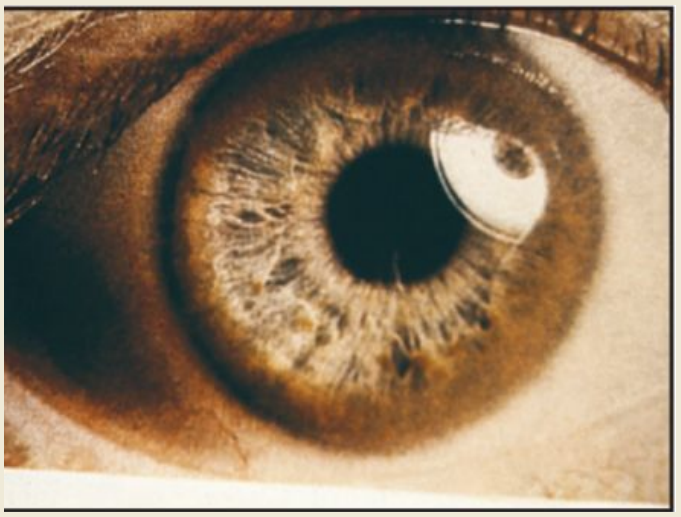
- This is a range of inherited conditions affecting the development of the intrahepatic biliary tree. Presentation is with liver cystic disease or fibrosis and renal disease.
- Congenital hepatic fibrosis presents in children over 2 years old with hepatosplenomegaly, abdominal distension, and portal hypertension. It differs from cirrhosis in that liver function tests are normal in the early stage. Liver histology shows large bands of hepatic fibrosis containing abnormal bile ductules.
- Complications include portal hypertension with varices and recurrent cholangitis.
- Cystic renal disease may coexist and may cause hypertension or renal dysfunction.
- Indications for liver transplant include severe recurrent cholangitis or deterioration of renal function requiring renal transplant, in which case a combined transplant would be offered.

Non-alcoholic fatty liver disease:

- Is the single most common cause of chronic liver disease in the high- income world. It is a spectrum of disease, ranging from simple fatty deposition (steatosis) through to inflammation (steatohepatitis), fibrosis, cirrhosis, and end-stage liver failure.
- In childhood, it may be associated with a metabolic syndrome or with obesity.
- The prognosis in childhood is uncertain; few develop cirrhosis in childhood in contrast to 8% to 17% of adults.
- They are usually asymptomatic, although some complain of vague right upper quadrant abdominal pain or lethargy.
- The diagnosis is often suspected following the incidental finding of an echogenic liver on ultrasound or mildly elevated transaminases carried out for some other reason. Liver biopsy demonstrates marked steatosis with or without inflammation or fibrosis.
- The pathogenesis is not fully understood but may be linked to insulin resistance.
- Treatment targets weight loss through diet and exercise, which may lead to liver function tests returning to normal.

Questions

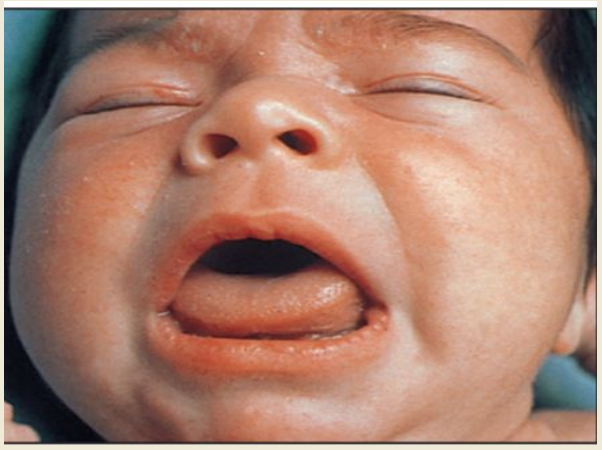
1- Summer, a 12-year-old girl, is seen in the Emergency Department. Her parents report that her school performance has been deteriorating and recently she has become confused and unsteady on her feet. Examination findings of her eyes are shown



Select the most likely diagnosis.
Select one answer only.
A. Glaucoma
B. Hyperthyroidism
C. Illicit drug use
D. Intracranial tumour
E. Wilson disease

2- Manuel, a 3-day-old infant is born to healthy parents. He presents with oozing from the umbilical stump and sleepiness. On examination he is pale and grunting. He responds only to painful stimuli. He has marked hepatomegaly. Oxygen is delivered and senior help summoned as he is very unwell. The nurse practitioner inserts an intravenous line and asks what blood tests you would like first. From the following list of blood tests pick the one you would undertake first.
Select one answer only.
A. Ammonia
B. Blood culture
C. Blood gas
D. Blood glucose
E. Coagulation studies

3- Javid is a 5-month-old Asian baby born at term in rural Pakistan. He presents with jaundice. His mother's blood group is AB rhesus positive. His stool and urine are a normal colour. He is breastfed, although he has not been feeding well. His mother is concerned that this could be due to his constipation. When you examine the infant you note that he has dry skin and an umbilical hernia.



Questions

4- Reece, a 4-week-old male infant living in the UK,is taken to his family doctor because he is jaundiced. He was born at term and is breastfed.His mother reports that he has always looked yellow and has started to develop bruises. His Stools are now pale in colour. On examination he has hepatomegaly. Which of the following investigations would you undertake first?
Select one answer only.
A. Faecal elastase
B. Serum conjugated and unconjugated bilirubin
C. Sweat test
D. Ultrasound scan of the liver
E. Urinalysis

5- Luna, a 32-year-old Cantonese woman has just given birth to her third child. She arrived in the UK 3 months ago to live with her extended family following the death of her husband. Antenatal screening shows that she is hepatitis B surface antigen (HBsAg) positive and hepatitis B e antigen (HBeAg) negative. The newborn infant looks well and has fed. The postnatal team are keen to send the mother and baby home.

Which of the following is the best advice to give concerning immunization of the family?
Select one answer only.

A. Hepatitis B vaccination for the baby
B. Hepatitis B vaccination for the baby and all other children
C. Hepatitis B vaccination for the baby and mother
D. Hepatitis B vaccination for the baby with hepatitis B immunoglobulin
E. No treatment required

Answers

1- **E.** Wilson disease
Correct. You are being shown Kayser-Fleischer rings from copper in the cornea. This is a very rare but treatable cause of liver failure/ neurological deterioration. Neuropsychiatric features are more common in those presenting from the second decade onwards and include deterioration in school performance, mood and behaviour change and extrapyramidal signs such as incoordination, tremor and dysarthria. A very rare diagnosis – a typical hospital in the UK will see one case every 30 years (it has an incidence of 1 in 200000).

2- **D.** Blood glucose
Correct. This must be done. Hypoglycaemia is an important consequence of serious illness including liver failure, e.g. from galactosaemia in view of his hepatomegaly and bleeding and sepsis. The priorities for management are:
• maintain blood glucose
• treat sepsis with broad-spectrum antibiotics
• prevent haemorrhage with intravenous vitamin K and fresh frozen plasma.

3- **E.** Hypothyroidism
Correct. Hypothyroidism is a cause of prolonged jaundice in infants. Clinical features include dry skin, constipation, coarse facial features including a large tongue as in the figure, umbilical hernia and a hoarse cry. In the UK it is usually identified on newborn biochemical screening (Guthrie test).

4- **B.** Serum conjugated and unconjugated bilirubin
Correct. This will enable you to identify whether, as the history suggests, this child has a conjugated hyperbilirubinemia. If this is the case then urgent further investigation is necessary as the child may have biliary atresia. Delay in diagnosis and definitive treatment adversely affects outcome.

5- **B** Hepatitis B vaccination for the baby and all other children
Correct. Prevention of hepatitis B virus infection is important. All pregnant women should have antenatal screening for HBsAg. Babies of all HBsAg-positive mothers should receive a course of hepatitis B vaccination (given routinely in many countries).