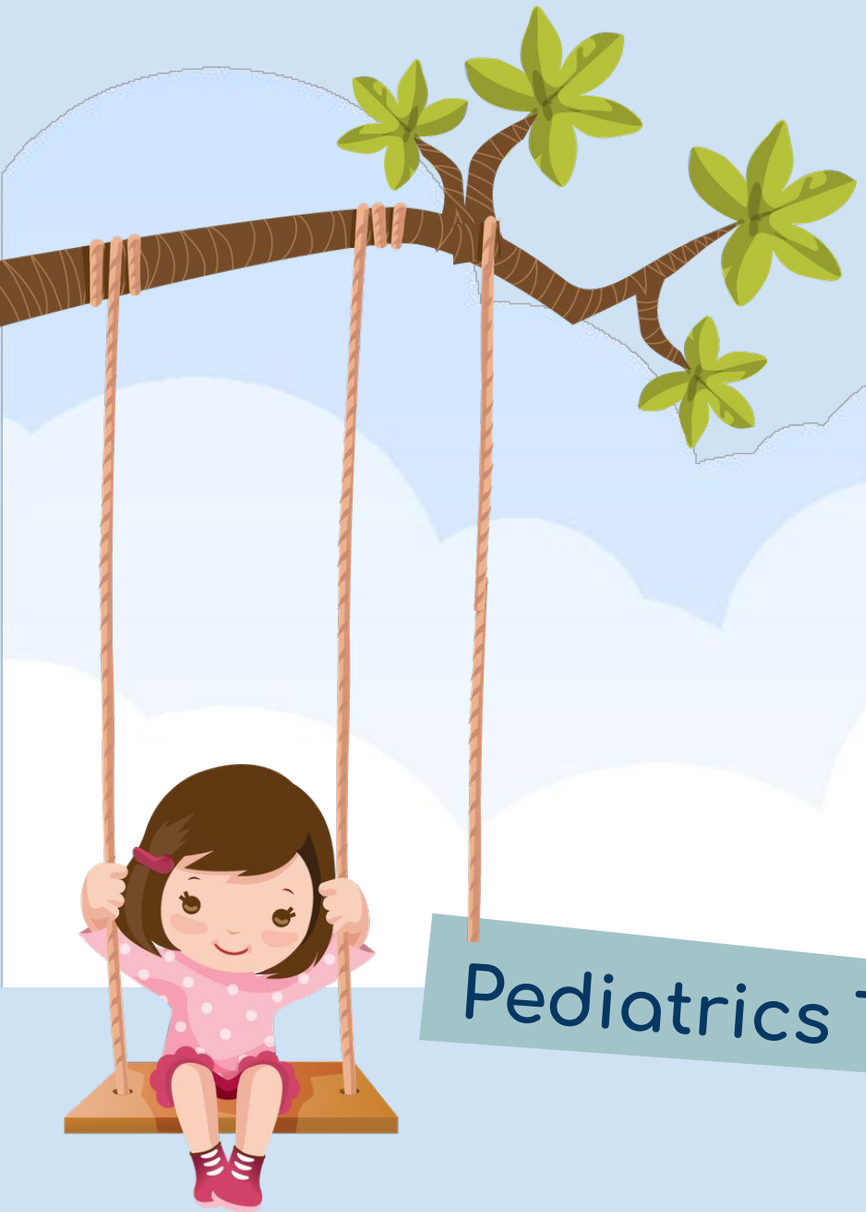

Pediatrics TeamWork 437

Liver Diseases

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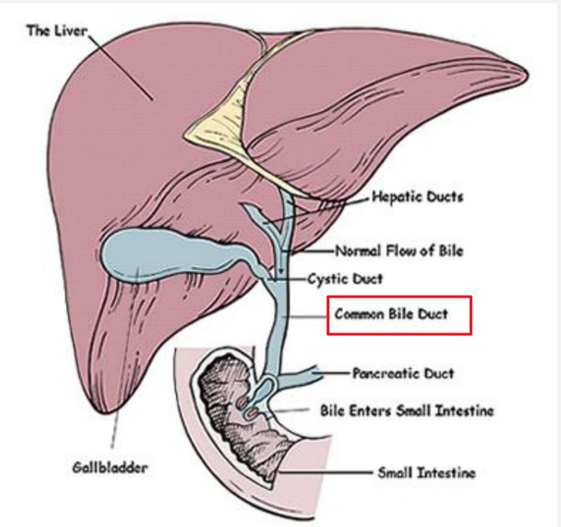
Objectives

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

Notes Previous Notes Book Important!

PART - 1
NORMAL ANATOMY & PHYSIOLOGY OF THE LIVER

Liver anatomy

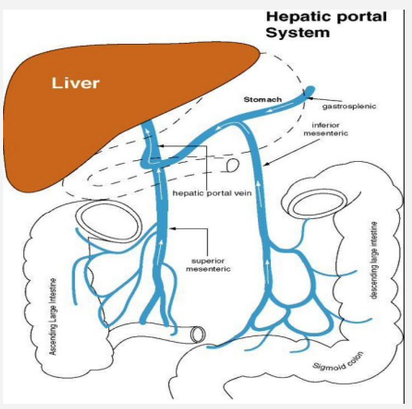


Liver blood supply

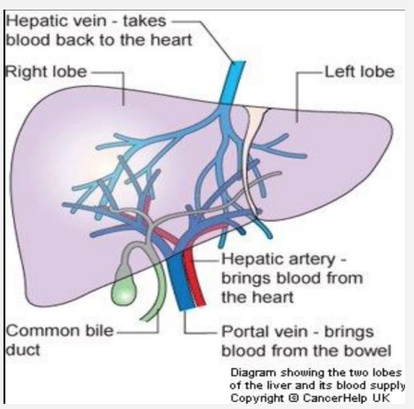
Liver has dual (bouble) Blood supply resources:

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.

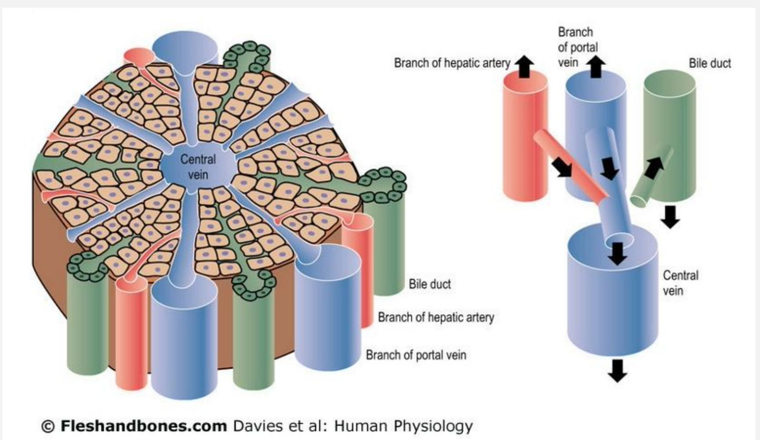
70% from portal vein
(nutrients)



30% from Hepatic artery
(oxygenated blood)



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**	1. Glucose. Glucose storage, converts glycogen to glucose in case of fasting. 2. Plasma proteins: (albumin, globulins, Clotting factors). All protein is from liver. In case of liver disease→edema and malnutrition. 3. Lipids: cholesterol and lipoproteins. Only some lipid is made in liver. Important for hormones. 4. Bile salts. Important for **fat absorption**.
Detoxification and excretion	1. Bilirubin 2. Ammonia converted to urea (urea cycle). Excreted in urine. 3. Drug metabolites 4. Cholesterol
Storage Function	1. Glucose→Glycogen. If high glucose it converts to glycogen. 2. Vitamins A, D, E, K and B12

Liver enzymes # LFTs

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

What are the liver function markers?

Don't reflect liver function

Enzymatic markers

- ALT (more specific) (Hepatocellular function)
- AST(Hepatocellular function) it has different sources such as **small bowel, RBCs** and **muscles**
- ALP (Biliary function) Can come from bones, **that's why it's high in kids and pregnant women from placenta**.
- GGT (more specific) (Biliary function)

Synthetic function markers

- Glucose
- Bilirubin
- Bile acids
- Albumin, Globulins
- Clotting factors (PT &PTT)
- Urea (from NH3 & AAs)

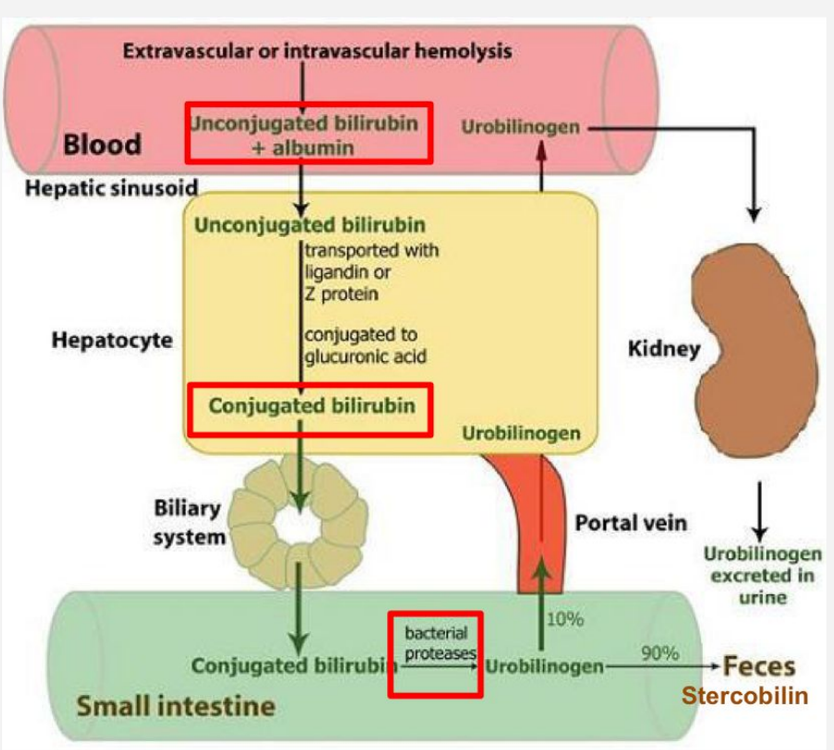
If only ↑ALP without other enzymes, it tells you that the source is not the liver.

Bilirubin metabolism

Very Important

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.
- **Clinically**= total **SBL** serum bilirubin level **> 5 mg/dl** (86 mmol/l)
- **Conjugated Hyperbili:** 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.

  EXCEPTIONS(Indirect hyperbilirubinemia but it's from the liver): Crigler Najjar syndrome and Gilbert syndrome.

Causes of unconjugated HB **(MCQs)**

Haemolysis

COOMB+ve

- ABO incompat., Rh incompat
- Autoimmune
- Drug-induced HA

COOMB - ve

- RBC membrane defects
- Hbpathy
- Enzyme defects (G6PD)
- HUS

Non-haemolysis

-Breast feeding/ Milk Jaundice
Most common cause.
How to differentiate?
Breastfeeding: occurs in the first few days of life, because milk is not enough causing dehydration and jaundice.
Breast milk: 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.
- Hypothyroidism. Slow feeder→ dehydration + thyroxine is important for the conjugation process. Can cause ↑ direct bili.
- Crigler Najjar syndrome
- Gilbert syndrome

Biochemical Patterns of liver diseases:

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

Isolated Hyperbilirubinemia Normal liver enzymes.			
Disease	**Defect**	**Manifestations**	**Treatment**
Indirect			
Gilbert's syndrome Presents at childhood and adolescence, harmless.	**Mutation in UGT1A1** (<30% of the normal activity)	**Mild** jaundice during **stress** fasting, illness	None
Crigler-Najjar syndrome type 1 Genetic disorder occurs in the first few days of life	**Mutation in UGT1A1** (absent activity)	**Severe** jaundice **(risk for kernicterus)** Permanent CNS insult	- Phototherapy for 17h a day. - Exchange transfusion if very severe. - Liver transplant only cure, only axillary transplant (small portion).
Crigler-Najjar syndrome type 2 Infants, milder form.	**Mutation in UGT1A1** (< 10% of the normal activity)	Mild- mod jaundice	Phenobarbitone Induces enzyme activity. Doesn't need transplant.
Direct both benign, present after delivery. Only need to know that 1- they present with mild HB 2. Gets better with time			
Dubin-Johnson syndrome	MRP2 receptor mutation (impair **transport** process across canalicular membrane)	No symptoms Neonatal cholestasis	None
Rotor syndrome	OTP1B1 & OTP1B3 mutation (affect **reuptake** of cong.Billi by hepatocytes)	No symptoms Neonatal cholestasis	None

Patterns for liver enzymes:

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

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

PART-2
Liver disease in children

- **Variable : age dependant**
    - **Infants:** Congenital and metabolic.
      Biliary atresia (BA), Neonatal hepatitis, metabolic liver disease, genetic disorders (progressive familial intrahepatic cholestasis (PFIC)
    - **Older children = adults liver diseases:**
      Viral Hepatitis, Wilson disease, Autoimmune hepatitis, etc...
- **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.

Cholestatic liver disease

Cholestasis ➡ **chole** = bile **Stasis** = stagnation

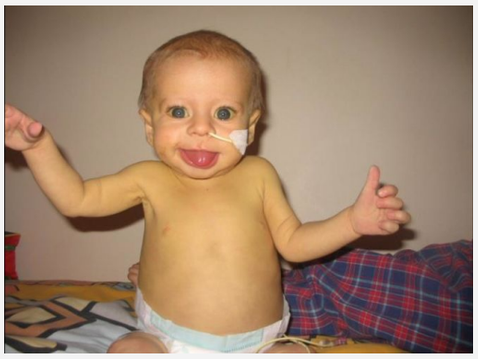
- The obstruction of bile flow either:
    - **Mechanical block** (biliary atresia, stones...) OR
    - **Functional block** (cellular **receptor** & **transporter** levels): e.g progressive familial intrahepatic cholestasis (PFIC) On U/S it's normal, More seen in infections , genetic/metabolic disorders, 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 could be severe enough to indicate liver transplant.
    - Cholesterol => xanthomas

Presentation of cholestasis

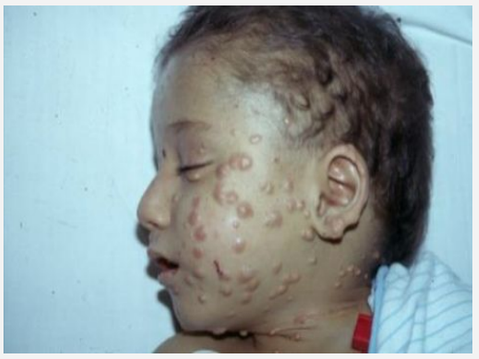
- **Jaundice** (accumulation of conjugated bilirubin)
- **Pale stool (Acholic stool)... Why? (MCQ)** Obstruction→bilirubin won't reach normal flora in colon→won't form urobilinogen→ pale stool.
- **Dark and foamy urine** (bile salts in the urine)+ bilirubin.
- **Pruritus** (accumulation of bile acids 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

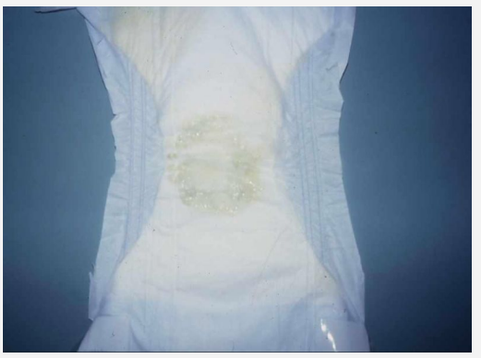
Jaundice+distention+muscle wasting + failure to thrive> need NGT feeding

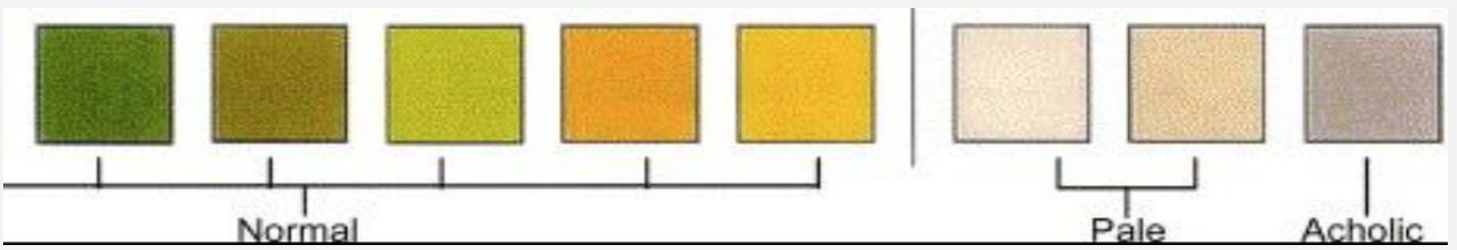


Xanthomas- alagille syndrome. Resolves with transplant and doesn't affect CVS.



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

STEP 1 — **Confirm the presence of cholestasis**
(**Clinically:** jaundice, acholic stool, pruritus, **& lab:** direct hyperbili+GGT)

STEP 2 IMP — **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 IMP — **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)

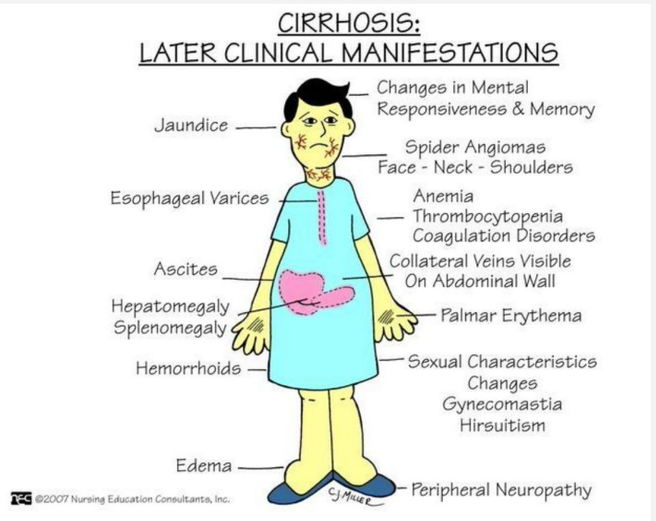
STEP 4 — **Further studies for other causes (genetic/metabolic)**

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/ALK Ph** (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.
- **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

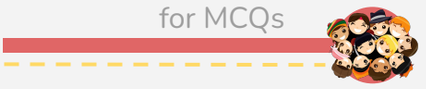
Idiopathic neonatal hepatitis and mimickers
- Cystic fibrosis
- Alpha 1-antitrypsin deficiency
- Hypopituitarism/hypothyroidism
- Neonatal iron storage disease

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)

PART-3 SPECIFIC LIVER DISEASES IN INFANTS Imp for MCQs



Biliary Atresia (BA)

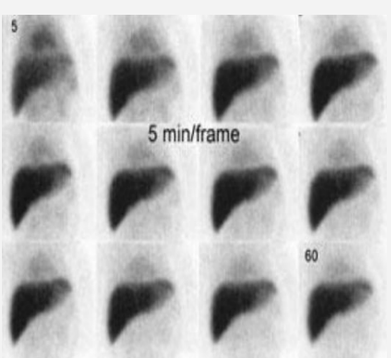
- Biliary atresia is an **<u>obstructive disease</u>** of the **biliary tree** (mainly extra-hepatic) secondary to idiopathic inflammatory/autoimmune process?? The theory is it's caused by intrauterine viral infection (CMV)
- It leads to **<u>gradual fibrosis</u>** and ultimate <u>obliteration of the biliary tract</u> -> <u>biliary cirrhosis</u> -> 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 **<u>first 2-6 weeks of life (MCQ)</u>**
- **Abdominal US:** <u>rule out other causes</u> of biliary **<u>obstruction</u>** (choledochal cyst congenital anomaly that affects biliary system, GB stones, biliary sludge (seen a suspected case in hospital read about it)...)
- **Hepatobiliary scintigraphy = nuclear scan (HIDA scan):** Not definitive
  - shows <u>good uptake</u> of tracer and <u>then NO excretion</u> into the intestine, even 24 hours later
  - We do it if pt presents early, needs long time to prepare, if late do biopsy.
- **A liver biopsy:** Not done anymore, feature not imp
  - confirms the diagnosis by revealing characteristic findings (proliferation of the interlobular bile ducts, periportal fibrosis, and bile plugs in canaliculi and ductules)
- <u>Definitive diagnosis</u> is confirmed by **Intra-operative cholangiogram**

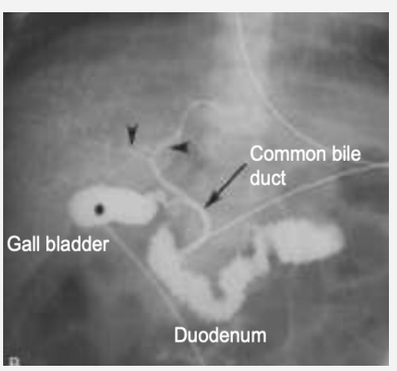
Hepatobiliary scintigraphy (HIDA scan)

NORMAL HIDA SCAN



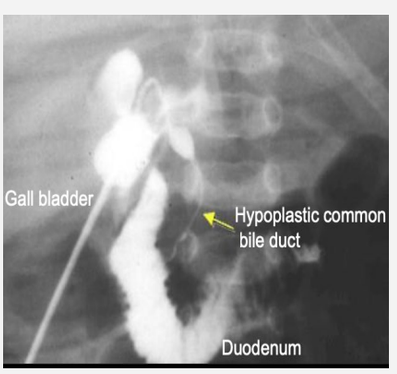
HIDA scan in BA patient

Intraoperative cholangiogram



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.

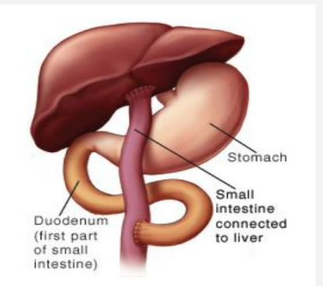
Normal study If normal next step is to take biopsy



Abnormal study (hypoplastic common bile duct) If abnormal next step is kasai procedure.

BA Management

- **Surgical correction (Kasai procedure or portoenterostomy) :**
- Remove biliary duct (fibrosed) connect jejunum to liver and duodenum
- 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)

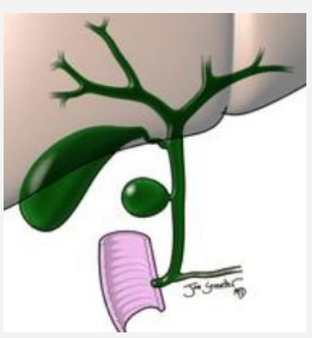


- **Liver transplantation** if:
  - Kasai failed, OR
  - Late presentation (> 3 months) OR
  - Decompensated liver disease

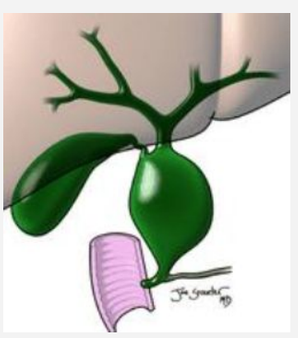
Choledocal cyst

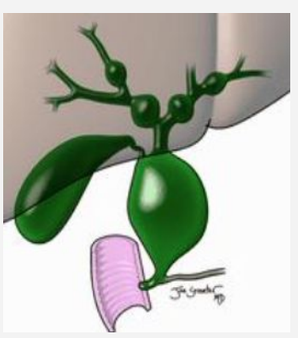
Ddx of biliary atresia, not imp.

- Cystic dilatation of the biliary tree at different levels -> **obstructive picture** Very common.
- **Present** same as BA with cholestasis picture, abdominal mass or asymptomatic, **biliary stones or risk for biliary carcinoma in adults** Cholangiocarcinoma.
- **Treatment:** surgical excision



Only resect cyst





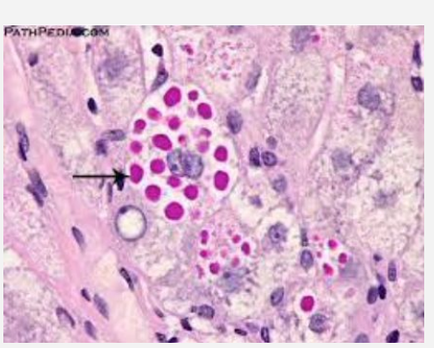
Have to resect the whole section

Alpha-1 Antitrypsin deficiency

- Elastase and trypsin are released from the body when lung cells are destroyed, when there's a deficiency 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:**
  - **Liver** disease (children or adults)
  - **Emphysema** lung disease (mainly seen in adults)
- AR disease (rare in our community)
  - Pi MM (normal) -> Pi ZZ (diseased) -> form abnormal A-1 AT protein -> **failed excretion from liver (trapped)** -> cholestatic liver disease. MZ > carrier.

Dx:

- A-1 AT level, phenotyping (pi ZZ) and
- confirmed with Liver biopsy (seen in special stain)
- Genetics



Treatment: supportive

Prognosis:

- variable (improve over time -> chronic liver disease

Neonatal Hepatitis

Condition that is not diagnosed, 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

Part 4
SPECIFIC LIVER DISEASES IN OLDER CHILDREN

Liver disease in older children = adults !!

Cause 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:

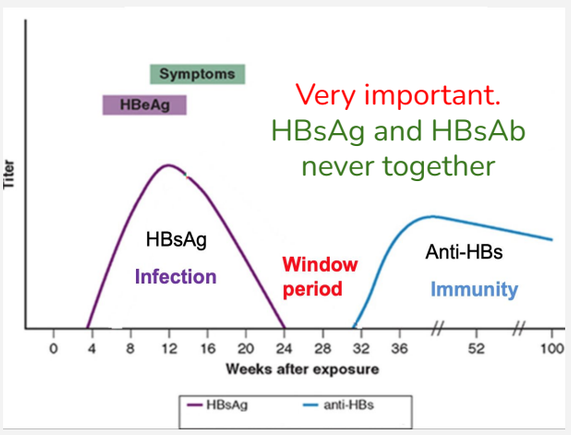
Flu-like illness , Anorexia, fever, vomiting, abdominal pain, darkening of the urine, **following ingestion of contaminated food or contact with infected patient** (oral-fecal route) Shouldn't go to school for 2 weeks.

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

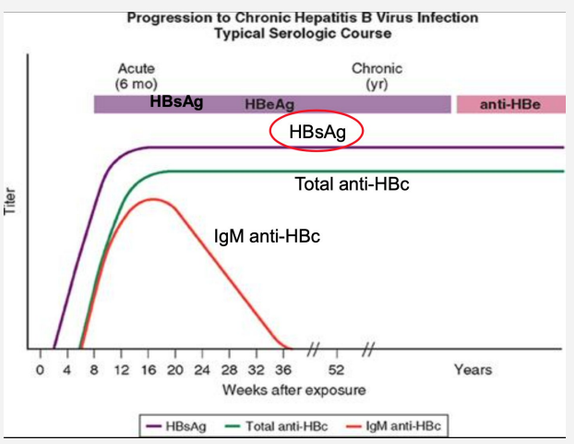
- **Diagnosis** of acute infection is based on the presence of anti-HAV IgM antibody in serum (MCQ) IgG>immunity
- The disease typically is **self-limited** in children and often is clinically not clear, In very rare cases, fulminant hepatic failure with severe necrosis of hepatocyte occurs and needs 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

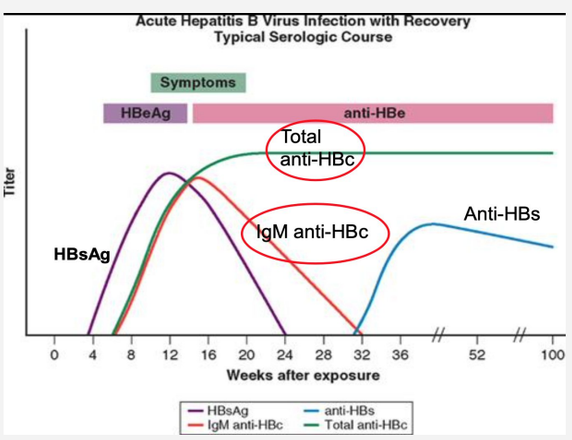
- Hepatitis B virus (HBV) infection can cause both acute and chronic hepatitis
- It can progress to cause **cirrhosis and hepatocellular carcinoma** if not treated (take long time to happen) Any cirrhosis can lead to cancer. HBV can also cause HCC without progressing into cirrhosis!!!!
- **Risk of transmission**: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



HBV serology markers



Chronic hepatitis



HBV serology markers..
recovery

Hepatitis B serological markers Important		
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 IgG Anti-HBC +
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

Vaccinated: anti-HBs +

Previously infected: both anti-HBc anti-HBs are +

High infectivity: HBeAg +

Low infectivity: HBeAb +

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: antiviral meds If the liver enzymes are normal> nothing, if ALT/AST are high> medication. Bad side effects and the course is mild.
  - ??? 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?) Below it mother's anti-HCV ab may still be in the blood.
- 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.
- **Prophylaxis**: no vaccine yet

Hepatitis D

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

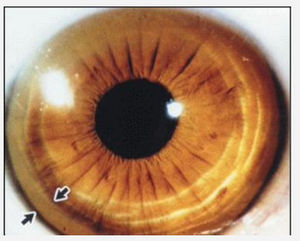
Hepatitis E

- 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 **(a must to know)**



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

- AR disorder
- Caused by a defect in biliary copper **excretion**
- **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 less 5 years because they did not reach sx phase.
- **Definitive diagnosis** requires evaluation of:
  - 24-hour **urinary** copper excretion AND
  - copper quantification in liver tissue obtained by **biopsy**
  - OR **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. In mild/asx we give zinc. Pyridoxine is given to prevent peripheral neuropathy
- **Early diagnosis = better prognosis** If not treated> cirrhosis

Take home messages

- Liver diseases are **not rare** in children & may present with variable presentations.Most commonly jaundice
- Any jaundiced baby who presents **after the age of 2 weeks** should be **investigated**
- Differentiation between **direct & indirect hyperbilirubinemia** can help in reaching the diagnosis quickly & effectively
- bc Pale looking **stool (acholic)** is a serious sign that needs an **urgent** evaluation
- **Early diagnosis & surgical intervention for biliary atresia** is the key for good long-term outcomes in these children.
- **Wilson** disease should be included in the differential diagnosis of **any child (> 5 yrs of age)** who presents with liver disease

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,**
- **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

- **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 phosphorylation	• Arthritis and erythema nodosum: liver disease with chronic inflammatory bowel disease
	• Arthritis, acne, fatigue: autoimmune hepatitis

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- Hepatomegaly is often present initially in biliary atresia
- A fasting abdominal ultrasound may demonstrate a contracted or absent gallbladder, though it may be normal (biliary atresia)
- Nutrition and fat soluble vitamin supplementation is essential in biliary atresia
- Choledochal cysts can be detected antenatally by US. They can present with neonatal jaundice and in older children with abdominal pain, palpable mass, jaundice or cholangitis
- Future complications of choledochal cyst include cholangitis and 2% risk of malignancy
- **Alagille syndrome:** triangular facies, skeletal abnormalities (butterfly vertebrae), congenital heart disease (classically peripheral pulmonary stenosis), renal tubular disorders and defects in the eye. Genetics to confirm diagnosis. Pruritus is profound and difficult to treat. Mortality is most likely secondary to heart disease
- **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. Progression of fibrosis is usual with most requiring liver transplantation
- **Galactosemia:** poor feeding, vomiting, jaundice, and hepatomegaly when fed milk. Liver failure, cataracts, and developmental delay are inevitable if it is untreated. Gram negative sepsis. Galactose in urine. The diagnosis is made by measuring the enzyme galactose-1-phosphate-uridyl transferase in red cells. A recent blood transfusion may mask the diagnosis. A galactose-free diet prevents progression of liver disease, but ovarian failure and learning difficulties may occur later.
- Large tender liver is common in viral hepatitis
- **Hepatitis A:** they can develop prolonged cholestatic hepatitis (self limiting). Close contacts should be vaccinated within 2 weeks.
- **Chronic hepatitis B:** Oral antiviral therapy such as entecavir and tenofovir are licensed for treatment in children >2 years and clears the virus in 25%. Long-term treatment may be required.
- When a viral aetiology of hepatitis is suspected but not identified, it is known as **seronegative hepatitis**.
- **Epstein-Barr virus:** Some 40% have hepatitis with marked hepatosplenomegaly, which may become fulminant. Less than 5% are jaundiced.
- **Acute liver failure:**

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
Gestational alloimmune liver disease	Autoimmune hepatitis

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 H_2-blocking drugs or proton pump inhibitors
- prevent cerebral oedema by fluid restriction and mannitol diuresis if oedema develops.

- **Features suggestive of poor prognosis in acute liver failure:** shrinking liver, rising bilirubin with falling transaminases, a worsening coagulopathy, or progression to coma
- Liver disease is the second most common cause of death after respiratory disease in cystic fibrosis.
- **Fibropolycystic liver disease:** 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

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- **Non-alcoholic fatty liver disease** is the single most common cause of chronic liver disease in the high- income world. In childhood, it may be associated with a metabolic syndrome or with obesity. Incidental finding of an echogenic liver on ultrasound or mildly elevated transaminases. Liver biopsy demonstrates marked steatosis with or without inflammation or fibrosis. Treatment targets weight loss through diet and exercise, which may lead to liver function tests returning to normal.
- **Complications of chronic liver disease:**

Encephalopathy

This occurs in end-stage liver disease and may be precipitated by gastrointestinal haemorrhage, sepsis, sedatives, renal failure, or electrolyte imbalance. It is difficult to diagnose in children as the level of consciousness may vary throughout the day. Infants present with irritability and sleepiness, while older children present with abnormalities in mood, sleep rhythm, intellectual performance and behavior disturbance. Plasma ammonia may be elevated and an EEG is always abnormal. Oral lactulose and a non-absorbable oral antibiotic (e.g. rifaximin) will help reduce the ammonia by lowering the colonic pH and increasing gut transit time.

Spontaneous bacterial peritonitis

This should always be considered if there is undiagnosed fever, abdominal pain, tenderness, or an unexplained deterioration in hepatic or renal function. A diagnostic paracentesis should be performed and the fluid sent for white cell count and differential and culture. Treatment is with broad-spectrum antibiotics.

Oesophageal varices

These are an inevitable consequence of portal hypertension and may develop rapidly in children. They are best diagnosed by upper gastrointestinal endoscopy. Acute bleeding is treated with blood transfusions and H_2-blockers (e.g. ranitidine) or omeprazole. Octreotide infusion, vasopressin analogues, endoscopic band ligation, or sclerotherapy may be effective. Portacaval shunts may preclude liver transplantation, but radiological placement of a stent between the hepatic and portal veins (transjugular intrahepatic portosystemic shunt, TIPS) can be used as a temporary measure if transplantation is being considered.

Ascites

Ascites is a major problem (Fig. 21.11). The pathophysiology of ascites is uncertain, but contributory factors include hypoalbuminaemia, sodium retention, renal impairment and fluid redistribution. It is treated by sodium and fluid restriction and diuretics. Additional therapy for refractory ascites includes albumin infusions or paracentesis.

Liver transplantation

Indications for liver transplantation in CLD:

- severe malnutrition unresponsive to intensive
- nutritional therapy
- complications refractory to medical management (bleeding varices, resistant ascites)
- failure of growth and development
- poor quality of life

Complications post transplantation include:

- primary non-function of the liver (5%)
- hepatic artery thrombosis (10%–20%)
- biliary leaks and strictures (20%)
- rejection (30%–60%)
- sepsis, the main cause of death.