University of Baghdad
College of Medicine

Title:Chronic liver disease (1)

Grade: Fifth year

Module: Pediatrics

Speaker: Professor Mohammad Fadhil Ibraheem

Learning objective

- Definition of Chronic liver disease
- Etiologies of chronic liver disease in children.
- Laboratory studies of CLD.
- Complications of chronic liver disease
- Indications, contraindications, and complications of transplantation in chronic liver failure.
- Liver cirrhosis definition, investigations and treatment.

Chronic liver disease

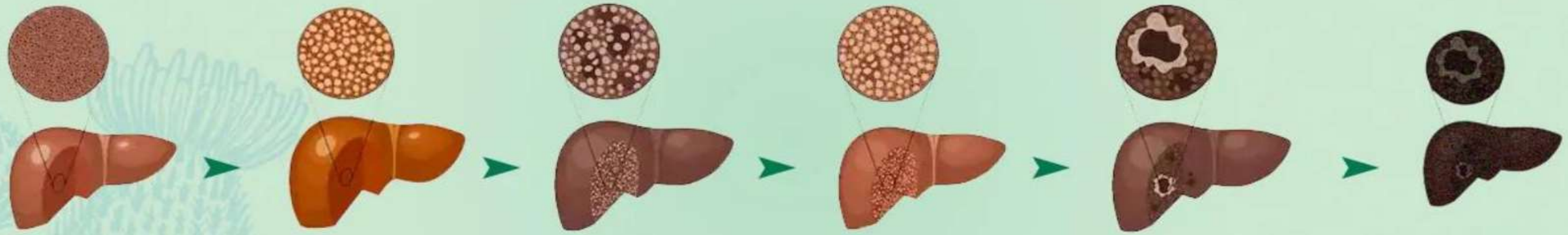
is defined as ongoing inflammation in the liver for **at least 6 months** with the potential to progress to cirrhosis and end-stage liver disease.
The etiologies of chronic liver disease are vast.

Progressive cholestatic liver diseases including biliary atresia and progressive familial intrahepatic cholestasis collectively are the primary indication for liver transplantation in children.

In these conditions, high concentrations of retained bile acids (>100 µmol/L) lead to hepatocyte oncotic swelling and ultimately necrosis. Locally injured hepatocytes then further propagate an inflammatory response mediated by released cytokines that lead to fibrosis and ultimately cirrhosis.

In conditions with lower concentrations of retained bile acids (25–100 µmol/L), cell apoptosis may play a primary role in liver injury.

DIFFERENT STAGES OF LIVER FAILURE



Healthy Liver

Inflammation

(Increase liver due to fat deposits)

Fibrosis

(Formation of scar tissue within in the liver)

Cirrhosis

(Scarred tissue replaces healthy tissue in the liver)

Liver Cancer

(Formation of malignant tumer in the liver)

End Stage Liver Disease

(Liver function ceased entirely)

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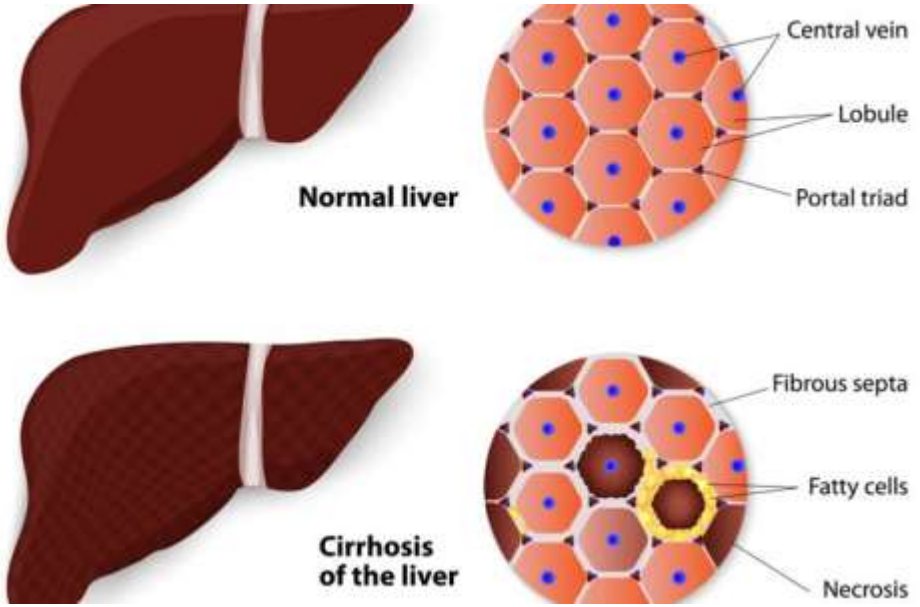
Hepatic stellate cells and portal myofibroblasts play a primary role in hepatic fibrosis, which progresses to bridging fibrosis and ultimately to cirrhosis.
Cirrhosis is the common end pathway for the majority of conditions that lead to chronic liver disease.



Etiologies of chronic liver disease in children.

1~ Biliary

- Extra-hepatic biliary atresia
- Cystic fibrosis
- Caroli disease and fibropolycystic disease
- Biliary obstruction: choledochal cyst, tumors
- Alagille syndrome
- Graft-versus-host disease
- Histiocytosis X
- Drugs
- Primary sclerosing cholangitis

2~Hepatic

1• Infectious

◦◦ neonatal hepatitis

◦◦ hepatitis B ± D

◦◦ hepatitis C

2• Immune

◦◦ autoimmune hepatitis types 1 and 2

◦◦ autoimmune sclerosing cholangitis ± inflammatory bowel disease

3• Nutritional

◦◦ non-alcoholic fatty liver disease (NAFLD)

◦◦ total parenteral nutrition induced cholestasis

4• Drugs/toxins

5• Genetic/metabolic

◦◦ α1-antitrypsin deficiency

◦◦ progressive familial intra-hepatic cholestasis

◦◦ Carbohydrate defects
  a. Galactosemia
  b. Hereditary fructose intolerance
  c. Glycogen storage disease types III and IV
◦◦ Amino acid defects
  – Tyrosinemia type 1
◦◦ Lipid storage diseases
  – Gaucher disease
  – Niemann–Pick disease type C
◦◦ Metal storage defects
  – Primary hemochromatosis
  – Wilson disease

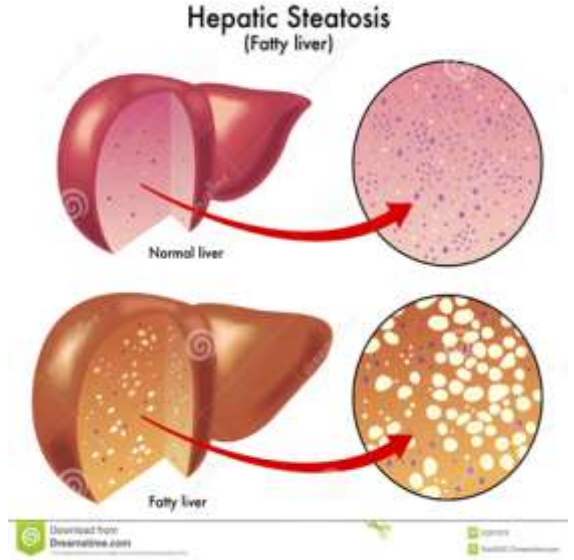
3-Vascular

- Cardiac: congestive heart failure, congenital cardiomyopathy, constrictive pericarditis
- Sinusoidal obstruction syndrome
- Budd–Chiari syndrome

Genetic metabolic disorders, including hereditary tyrosinemia, fatty acid oxidation defects, mitochondrial disorders, cystic fibrosis, and Wilson disease, all have hepatic steatosis in addition to cholestasis in the liver.

(**Steatosis** is defined as a reversible intrahepatic fat of at least 5% of liver weight.

Simple accumulation of triacylglycerols in the liver could be hepatoprotective; however, prolonged hepatic lipid storage may lead to liver metabolic dysfunction, inflammation, and advanced forms of nonalcoholic fatty liver disease.



Clinical presentation and diagnosis of chronic liver disease

Physical examination may show the following:

1• No signs or symptoms of chronic liver disease.

2• Jaundice, ascites, splenomegaly, growth failure, xanthomas, spider nevi, cyanosis, palmar erythema, and clubbing.

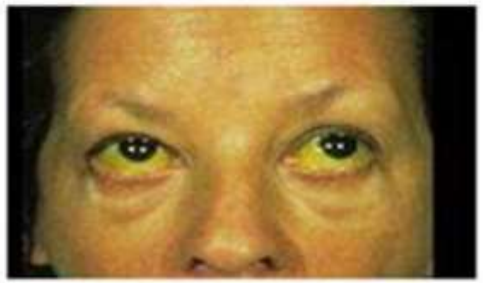
3• Either hepatosplenomegaly or a shrunken hard nodular liver with splenomegaly may be present.

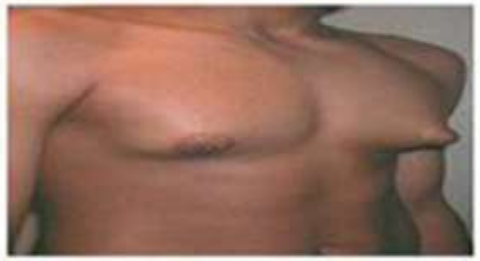
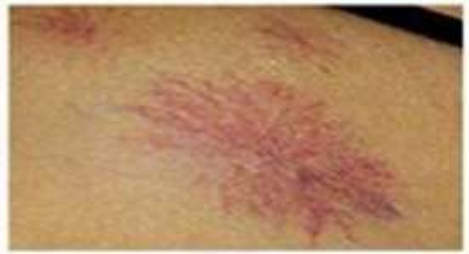
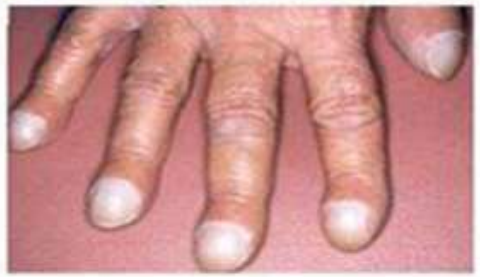
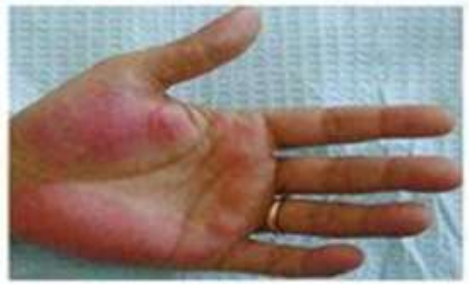
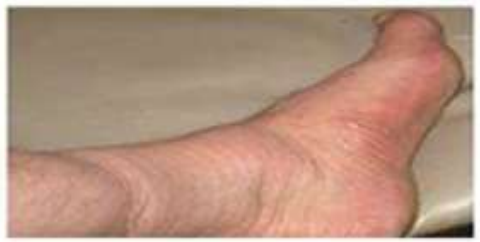
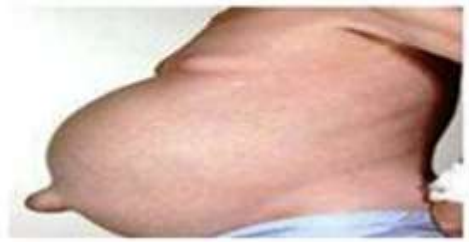
4• Patients with cholestatic liver disease may also present with pruritus, dark urine, and acholic stools in addition to jaundice.

5• Signs of hepatic encephalopathy may be subtle in children and are described later.

6• Non-specific clinical symptoms may include anorexia, fatigue, nausea, vomiting, or abdominal pain.

Signs of CLD



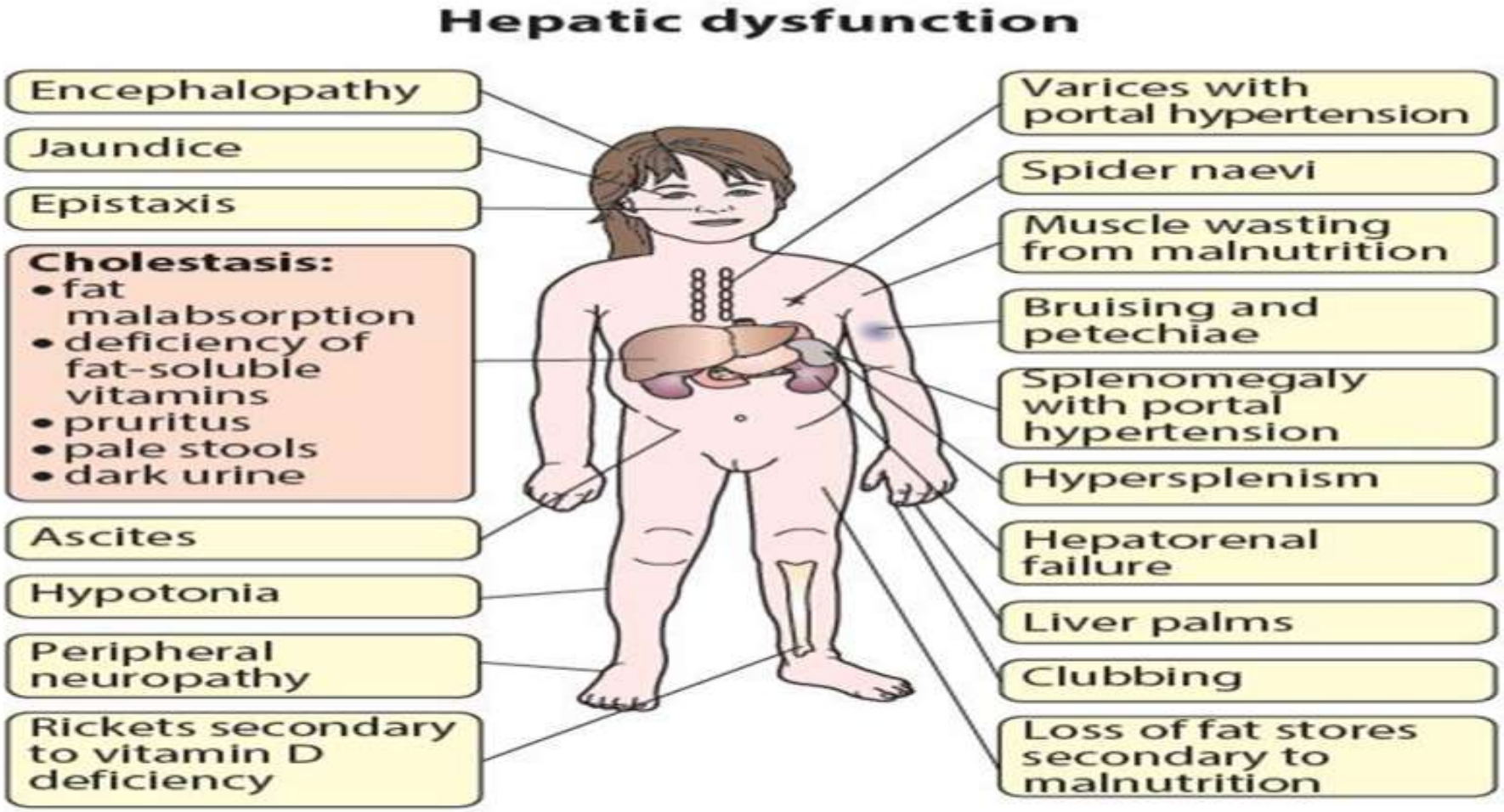
Effects of portal hypertension

- Esophageal varices
  - Hematemesis
  - Gastropathy
- Melena
- Splenomegaly
- Dilated abdominal veins (caput medusae)
- Ascites
- Rectal varices (hemorrhoids)

Effects of liver cell-failure

- Coma
- Fetor hepaticus (breath smells like a freshly opened corpse)
- Spider nevi
- Gynecomastia
- Jaundice
- Ascites
- Loss of sexual hair
- Testicular atrophy
- Liver flap (coarse hand tremor)
- Bleeding tendency (decreased prothrombin)
- Anemia
  - -Macrocytic
  - -Iron deficiency (blood loss)
- Ankle edema

• The dramatic presentation of new-onset hematemesis Secondary to variceal bleeding may also be the first sign of chronic liver disease in a previously undiagnosed patient.



Clinical features of liver disease. In addition, these children may have growth failure and developmental delay.

Laboratory studies in CLD may reveal:

- Elevated transaminases (ALT, AST)

~ [**ALT normal value 10 – 40 IU/I this enzyme is found mainly in the liver.**
Smaller amounts of ALT are in the kidneys, heart, muscles, and pancreas].

~ [AST **normal value 10 – 40 IU/I this enzyme is found mainly in the liver, heart, kidney and skeletal muscles. It is also found in lesser amounts in other tissues**].

- Bilirubin [**Bilirubin is a brownish yellow substance found in bile. It is produced when the liver breaks down old red blood cells. Bilirubin is then removed from the body through the stool (feces) and gives stool its normal color, Reference Values : ≤1.0 mg/dl, with direct TSB: 0.0-0.3 mg/dL].**

- γ-glutamyl transferase (GGT)[normal value 5 – 55 IU/L, it is used to differentiate between liver and bone disease as a cause of elevated alkaline phosphatase although it may rise in conditions other than liver disease e.g. **congestive heart failure**, **diabetes**, **drugs** like phenytoin and phenobarbital],

- Alkaline Phosphatase (ALP) **[The normal range is 44 to 147 international units per liter (IU/L) High levels can occurs in liver and bone disease].**

- Ammonia.

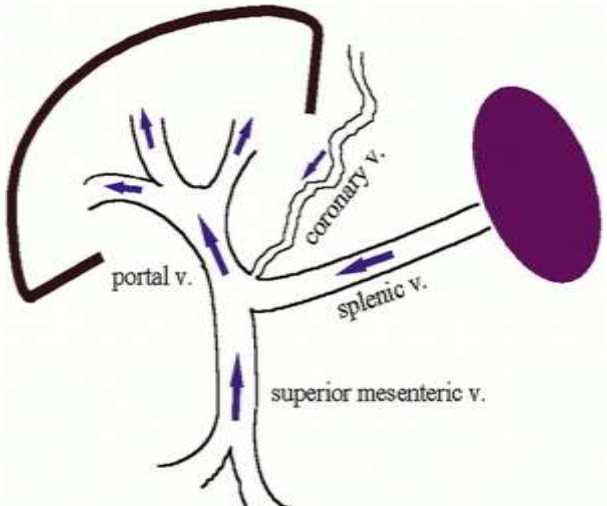
- Hypersplenism may be suggested by thrombocytopenia, anemia, and leukopenia.
- Evidence of renal dysfunction may also be noted i.e. hepatorenal syndrome (HRS).

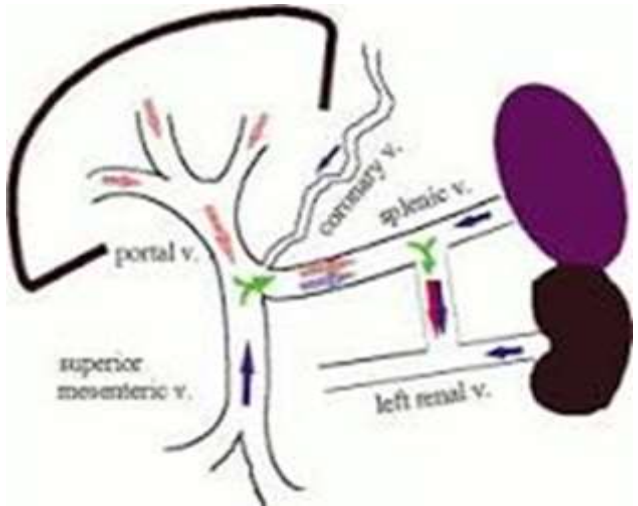
• In decompensated chronic liver disease, abnormal hepatic synthetic function is denoted by hypoalbuminemia and a prolonged international normalized ratio (INR).

• An abdominal ultrasound may reveal splenomegaly and ascites.
An abdominal ultrasound with Doppler will assess patency of the portal vein and identify hepatofugal flow patterns

(Hepatofugal flow (ie, flow directed away from the liver) is abnormal in any segment of the portal venous system and is more common than previously believed. Hepatofugal flow can be demonstrated at angiography, Doppler ultrasonography (US), magnetic resonance imaging, and computed tomography (CT). is clinically important for diagnosis of portal hypertension, for determination of portosystemic shunt patency and overall prognosis in patients with cirrhosis. other etiologies such as congestive heart failure and acute liver failure can be responsible for the same ultrasound findings

(- Hepatopetal denotes **flow of blood towards the liver**,which is the normal direction of blood flow through the portal vein).





- Contrast-enhanced cross-sectional imaging with a computed tomography (CT) or magnetic resonance imaging (MRI) may identify portal vein thrombosis or Budd–Chiari syndrome.
- Magnetic resonance cholangiopancreatography (MRCP) may additionally identify anatomic abnormalities of the biliary tree.
- Echocardiogram can reveal cardiac abnormalities that lead to chronic liver disease.
- A liver biopsy is necessary to confirm the presence of fibrosis and cirrhosis and may clarify the underlying etiology of chronic liver disease. However, with progression to cirrhosis, distinguishing histopathologic features characteristic of the underlying diagnosis may be masked.

With few exceptions, such as in Wilson disease, chronic hepatitis B and C, and autoimmune hepatitis, there are **no** medications or interventions that halt the progression to uncompensated cirrhosis.

The underlying principle of treatment in patients with chronic liver disease is to anticipate, prevent, identify, and ultimately manage complications in these patients.

Age-specific investigations in chronic liver disease.

Age of patient Investigation

Neonate

TORCHES screen

Galactose 1-phosphate uridyl transferase

Free T4, TSH, morning cortisol

Targeted DNA mutational analysis

Sweat test (>4 weeks)

Older child (>2 years)

Copper, ceruloplasmin, urinary copper, C3, C4, ANA, SMA, LKM, immunoglobulins, EBV

If indicated :- Liver biopsy for: histology, electron microscopy, enzyme analysis, immunohistochemistry, culture, copper concentration Skin biopsy, ophthalmology, cardiology, bone marrow aspirate Endoscopy, ERCP.

Complications of chronic liver disease

1- Nutrition

Effective nutrition is essential. It may improve and stabilize patients with liver disease. Barriers to effective nutrition include:

-**Fat malabsorption** – long chain fat is not effectively absorbed without bile. Therefore, medium chain triglyceride containing milk (special formula) is required if children are persistently cholestatic, as it does not require bile micelles for absorption.

Up to 40% of fat needs to be long chain fat to prevent essential fatty acid deficiency.

-**Fat-soluble vitamins** are carried on the long chain fats and hence deficiency is common unless these vitamins are supplemented protein malnutrition – poor intake combined with high catabolic rate of the diseased liver makes protein malnutrition common at presentation of liver disease.

-**Protein** intake should not be restricted unless the child is encephalopathic.

2~ Fat~soluble vitamins

All fat~soluble vitamins can be given orally.
In severe deficiency, intramuscular administration may be required.

3~ Pruritus

Severe pruritus is associated with cholestasis, although the aetiology is not clear. Pruritis is difficult to manage and may lead to excoriation of the skin.
Treatment includes:

- Loose cotton clothing, avoiding overheating, keep nails short.
- Moisturizing the skin with emollients.
- Medication: phenobarbital to stimulate bile flow; cholestyramine, a bile salt resin to absorb bile salts;

Urso deoxycholic acid, an oral bile acid to solubilize the bile; rifampicin, an enzyme inducer.

4~ Encephalopathy

This occurs in end-stage liver disease and may be precipitated by gastrointestinal hemorrhage, sepsis, sedatives, renal failure, or electrolyte imbalance.

It is difficult to diagnose in children as the level of consciousness may vary throughout the day.

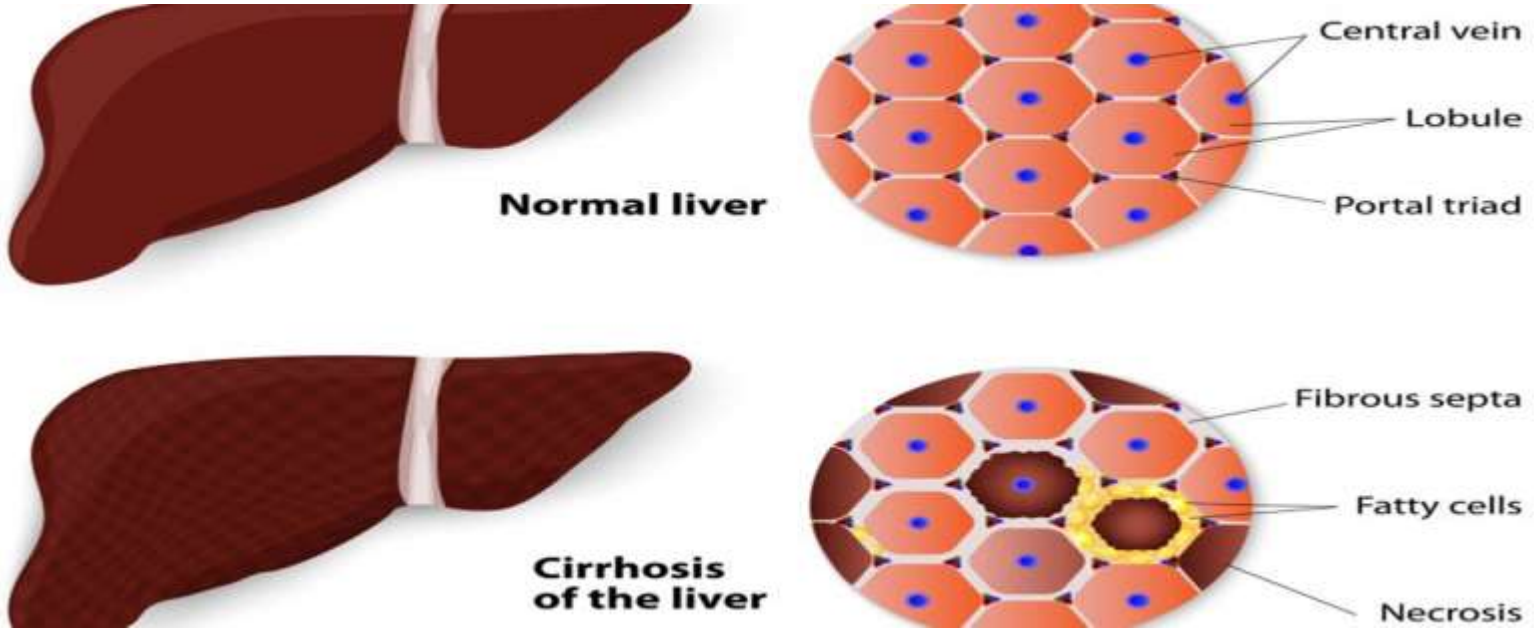
Infants present with irritability and sleepiness, while older children present with abnormalities in mood, sleep rhythm, intellectual performance, and behavior.

Plasma ammonia may be elevated and an EEG is always abnormal.

Oral lactulose and a nonabsorbable oral antibiotic (e.g. rifaximin) will help reduce the ammonia by lowering the colonic pH and increasing gut transit time.

5~ Cirrhosis and portal hypertension

Cirrhosis is the end result of many forms of liver disease.
It is defined pathologically as extensive fibrosis with regenerative nodules.
It may be secondary to hepatocellular disease or to chronic bile duct obstruction (biliary cirrhosis).
The main pathophysiological effects of cirrhosis are diminished hepatic function and portal hypertension with splenomegaly, varices, and ascites.
Hepatocellular carcinoma may develop.



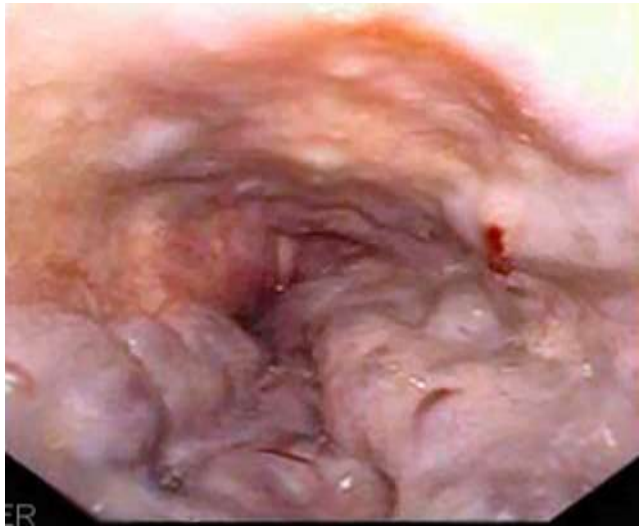
6~ Oesophageal varices

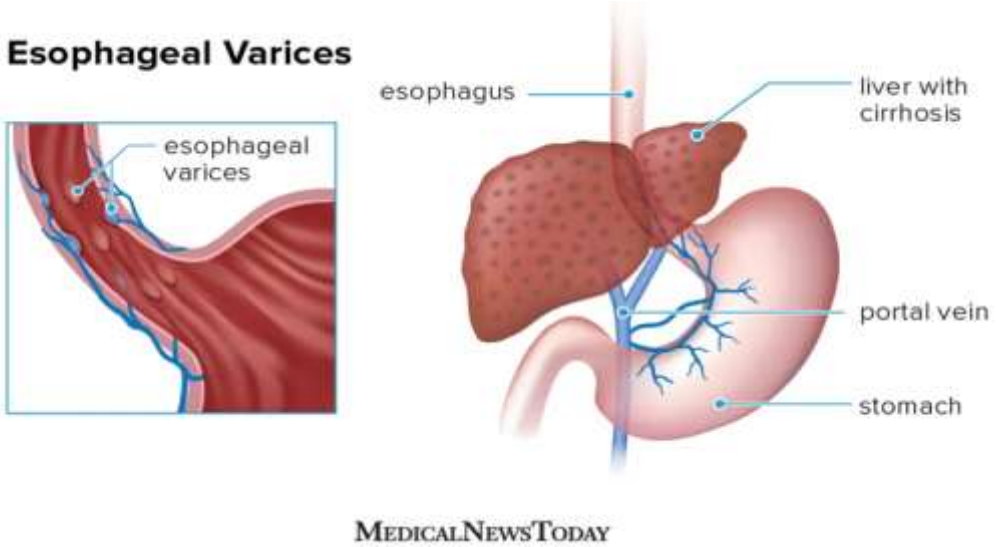
These are an inevitable consequence of portal hypertension and may develop rapidly in children. They are best diagnosed by upper gastrointestinal endoscopy.

Acute bleeding is treated conservatively with blood transfusions and H2-blockers (e.g. ranitidine) or omeprazole.

If bleeding persists, octreotide infusion, vasopressin analogues, endoscopic band ligation, or sclerotherapy may be effective.

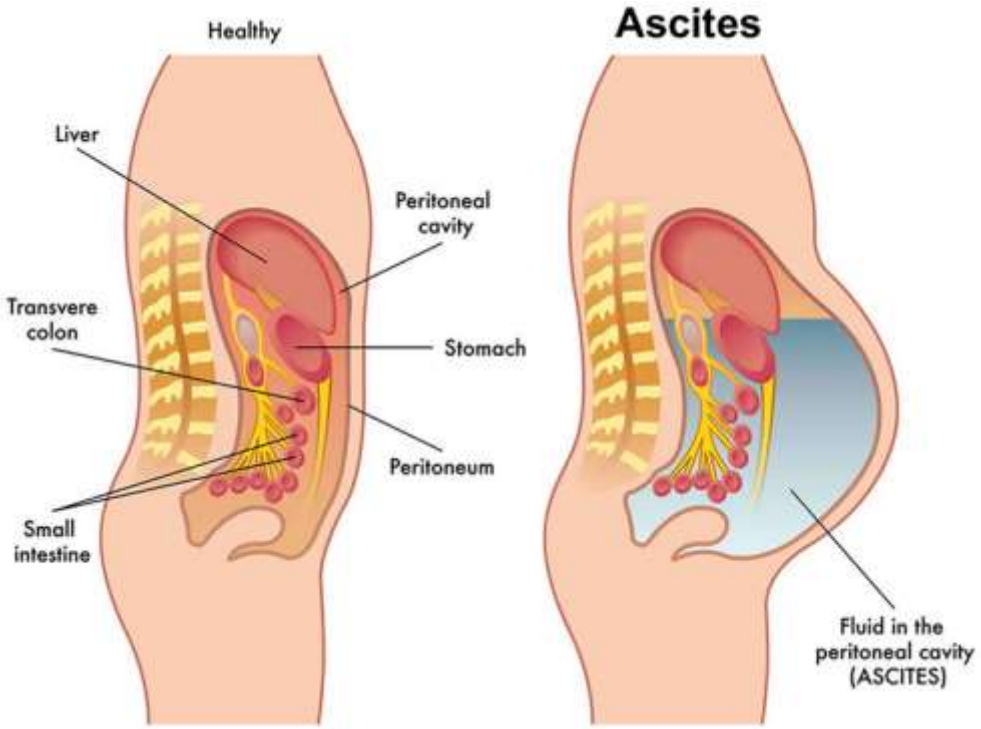
Portacaval shunts may preclude liver transplantation, but radiological placement of a stent between the hepatic and portal veins can be used as a temporary measure if transplantation is being considered.





7~ Ascites

Ascites is a major problem. 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.



8~ 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.

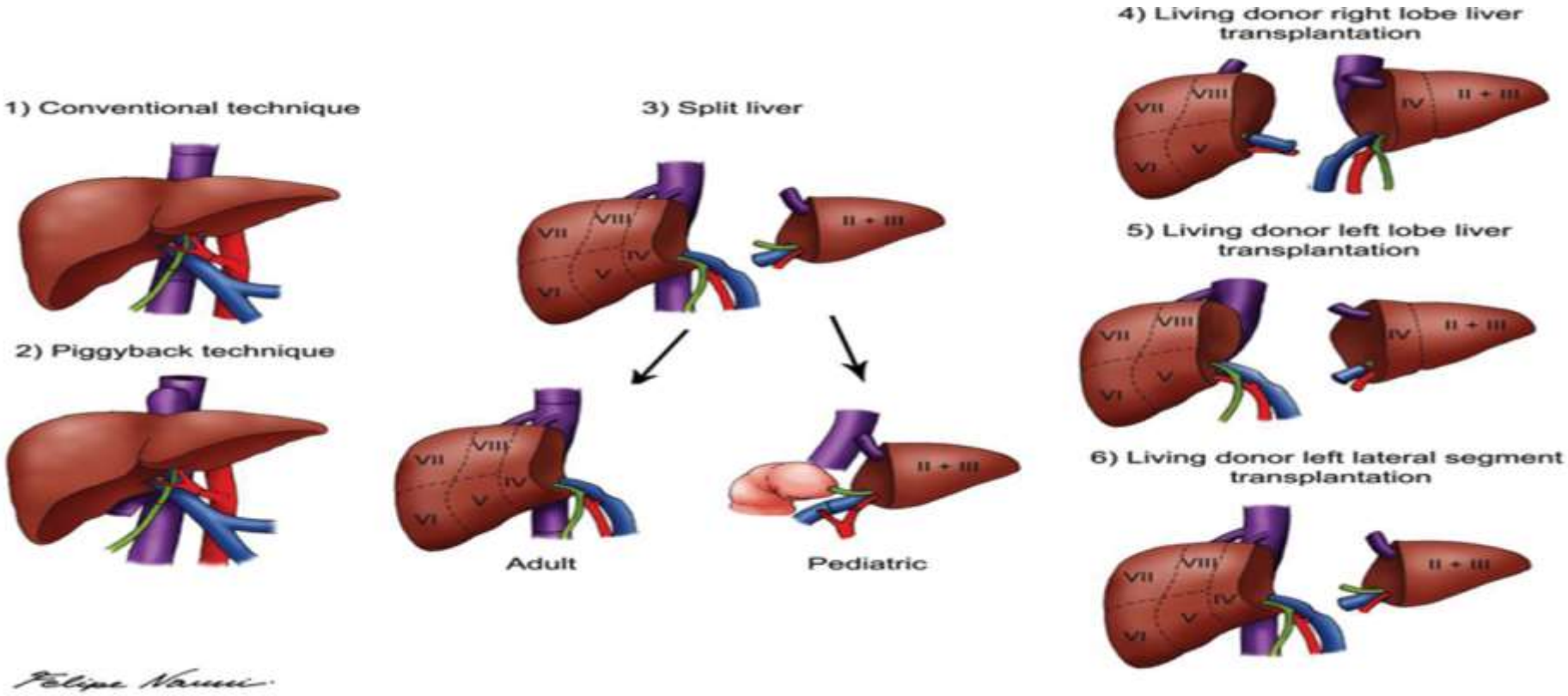
Treatment is with broad-spectrum antibiotics.

9~ Renal failure

This may be secondary to renal tubular acidosis, acute tubular necrosis, or functional renal failure (hepatorenal syndrome).

Liver transplantation

Liver transplantation is an accepted therapy for acute or chronic end-stage liver failure and has revolutionized the prognosis for these children. Transplantation is also considered for some hepatic malignancy (hepatoblastoma or hepatocellular carcinoma).



Indications for transplantation in chronic liver failure:

1• Severe malnutrition unresponsive to intensive nutritional therapy.

2• Complications refractory to medical management (bleeding varices, resistant ascites).

3• Failure of growth and development.

4• Poor quality of life.

Liver transplant evaluation includes assessment of the vascular anatomy of the liver and exclusion of irreversible disease in other systems.

Absolute contraindications include:

Sepsis, untreatable cardiopulmonary disease or cerebrovascular disease.

There is considerable difficulty in obtaining small organs for children. Most children receive part of an adult's liver, either a cadaveric graft or from a living related donor.

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).

In large national centres, the overall 1-year survival is approximately 90%, and the overall 20-year survival is greater than 80%.

Most deaths occur in the first 3 months.

Children who survive the initial postoperative period usually do well.

Long-term studies indicate normal psychosocial development and quality of life in survivors.

The effects of fat-soluble vitamin deficiency

Vitamin K……. Bleeding diathesis including intracranial bleeding.

Vitamin A……. Retinal changes in infants and night blindness in older children.

Vitamin E…….. Peripheral neuropathy, haemolysis, and ataxia.

Vitamin D…….. Rickets and fractures.

Liver cirrhosis

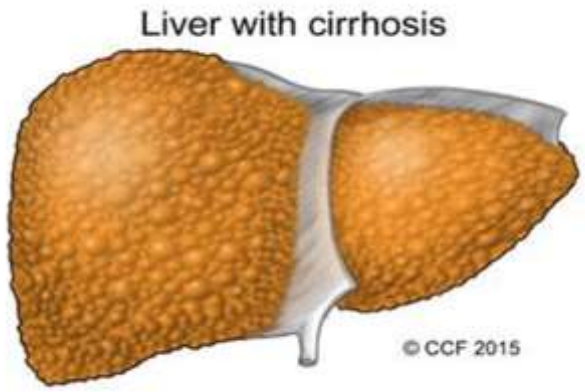
Cirrhosis is a late-stage result of liver disease and its complications, in which healthy liver tissue is replaced with scar tissue and the liver is permanently damaged.

This is followed by cell repair and finally tissue scarring as a result of the repair process.

You may not have symptoms in the beginning stages of the disease.

In infants, cirrhosis is most often caused by **biliary atresia** and **genetic-metabolic diseases**, while in older children, it tends to result from **autoimmune hepatitis**, **Wilson's disease**, **alpha-1-antitrypsin deficiency** and **primary sclerosing cholangitis**.

The scar tissue blocks the flow of blood through the liver and slows the liver's ability to process nutrients, hormones, drugs and natural toxins (poisons).



STAGES OF LIVER CIRRHOSIS

1. HEALTHY LIVER

<5% OF FATTY LIVER CELLS

2. HEPATIC STEATOSIS

FAT DEPOSITS CAUSES LIVER ENLARGEMENT

3. STEATOHEPATITIS (NASH)

STEATOSIS INFLAMATION BALOONING

4. LIVER FIBROSIS

STEATOSIS INFLAMATION BALOONING FIBROSIS

5. LIVER CIRRHOSIS

SCAR TISSUE REPLACES LIVER CELLS

It also reduces the production of proteins and other substances made by the liver.
Cirrhosis eventually keeps the liver from working properly.
Late-stage cirrhosis is life-threatening.

The symptoms of cirrhosis in children and adolescents are similar to those of adults.
However, in pediatric patients, the first sign of cirrhosis is often **poor weight gain.**

The complications of pediatric cirrhosis include:

Gastrointestinal bleeding caused by gastroesophageal varices, ascites and spontaneous bacterial peritonitis.

Children with compensated cirrhosis may be asymptomatic if liver function is adequate.
They will not be jaundiced and may have normal liver function tests.

As the cirrhosis increases, however, the results of deteriorating liver function and portal hypertension become obvious.

Physical signs include jaundice, palmar and plantar erythema, telangiectasia and spider naevi, malnutrition, and hypotonia.
Dilated abdominal veins and splenomegaly suggest portal hypertension, although the liver may be shrunken and impalpable.

In pediatric patients, special attention should be paid to the nutritional alterations caused by cirrhosis, since children and adolescents have higher nutritional requirements for growth and development.

Children and adolescents with chronic cholestasis are at risk for several nutritional deficiencies.

The treatment of cirrhosis-induced portal hypertension in children and adolescents is mostly based on methods developed for adults.

Treatment depends on the cause of cirrhosis and how much damage exists.

Investigations:

1• Screening for the known causes of chronic liver disease

2• Upper gastrointestinal endoscopy to detect the presence of oesophageal varices and/or erosive gastritis

3• Abdominal ultrasound – may show a shrunken liver and splenomegaly with gastric and oesophageal varices

4• Liver biopsy – may be difficult because of increased fibrosis but may indicate the aetiology (e.g. typical changes in congenital hepatic fibrosis, copper storage).

As cirrhosis decompensates, biochemical tests may demonstrate an elevation of aminotransferases and alkaline phosphatase. The plasma albumin falls and the prothrombin time becomes increasingly prolonged.

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