Liver Cirrhosis

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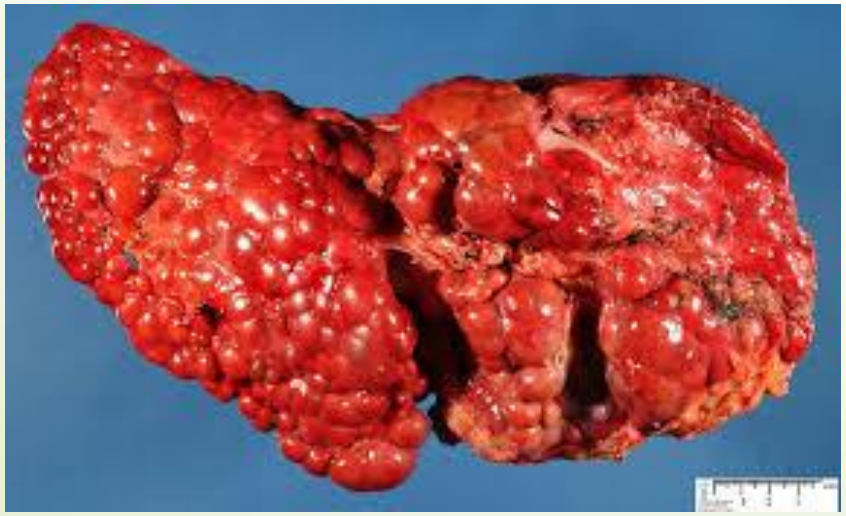
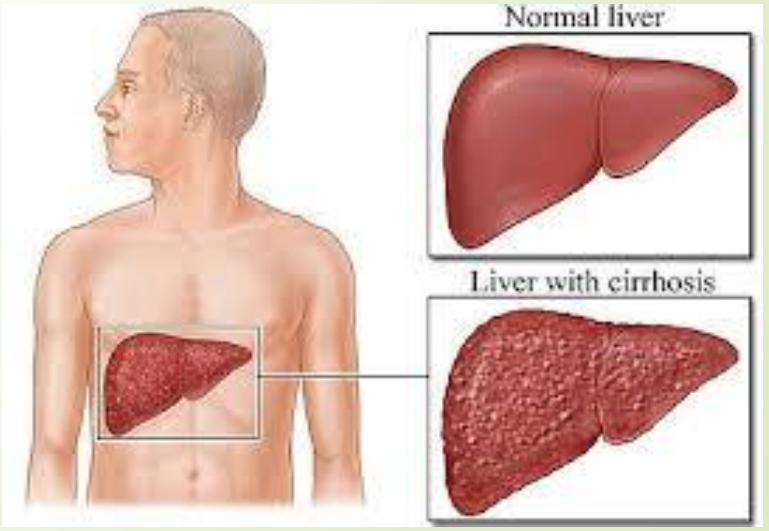
Background

- **Cirrhosis** is the conversion process of normal hepatocyte into structurally abnormal nodules. Consequently, leading to hepatocytes destruction and replacement by **fibrous tissue**.

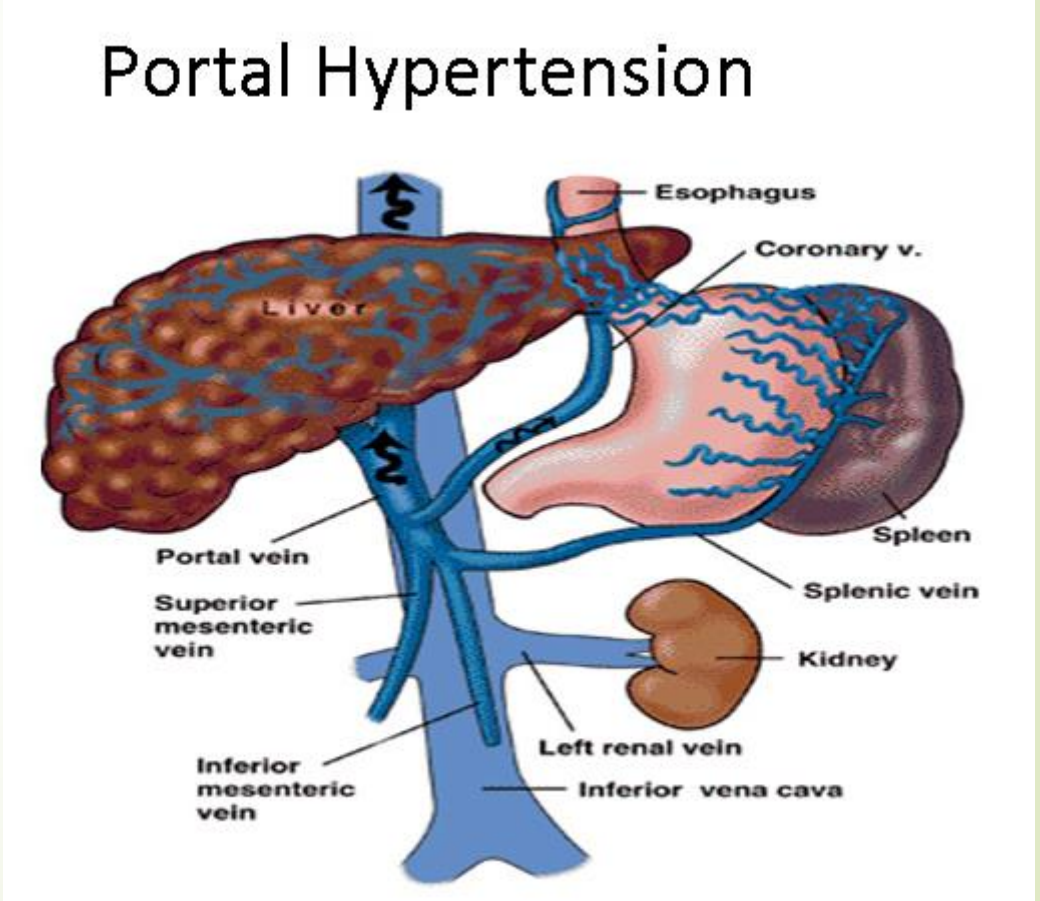
- The number of normally functioning liver cells **reduces further**, because of continued hepatocyte death, the **clinical condition deteriorates progressively** with the development of liver failure.





Background

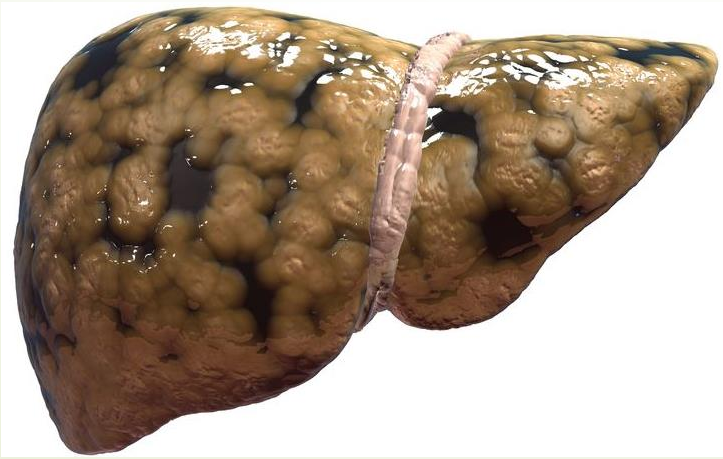
- The anatomical changes within the liver **increase resistance to blood flow** from the portal system, causing an increase in pressure within this system resulting in **portal hypertension**, one of the major complications of cirrhosis.



Etiology of Cirrhosis

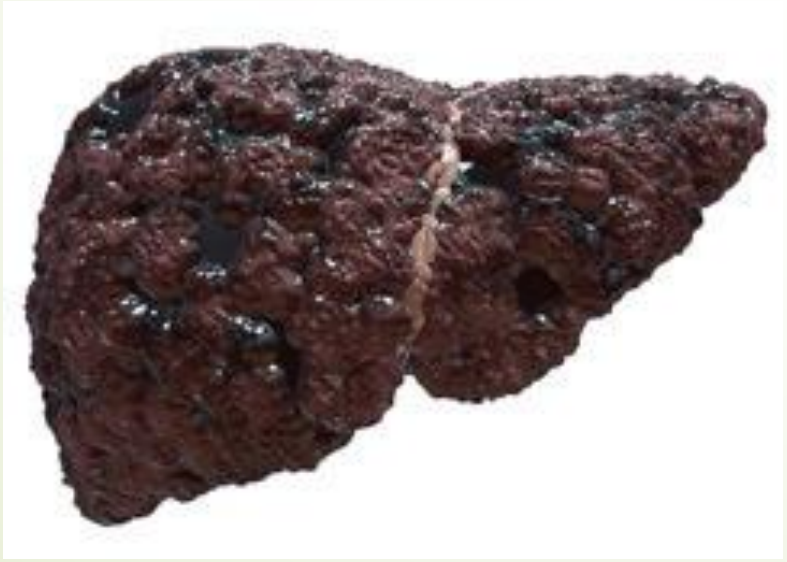
- **Alcohol** is the single most significant cause of **liver disease** throughout the Western world accounting for between **40%** and **60%** of cases of cirrhosis in different countries.

- **Liver disease** related to **recent alcohol consumption** presents a broad spectrum, ranging from the **benign fatty liver disease** to **alcoholic hepatitis**, a condition with an immediate mortality of between 30% and 60%.



Alcohol

- An estimated **20% of alcohol abusers** develop progressive liver fibrosis, which can eventually lead to **alcoholic cirrhosis**, typically after a period of **10–20 years of heavy indulgence**.



Etiology of Cirrhosis

- **Viral hepatitis B, C, D.**
- **Drugs** including Isoniazid, methyldopa, methotrexate, phenothiazine, estrogen, anabolic steroids, amiodarone.
- **Nonalcoholic fatty liver**: is very similar to alcohol-induced disease is now well recognized in a number of settings including
  - obesity
  - diabetes mellitus
  - metabolic syndrome

Etiology of Cirrhosis

- **Autoimmune hepatitis:** is an un-resolving inflammation of the liver characterized by the presence of **auto-antibodies**. It is usually a chronic, progressive disease which can occasionally present acutely with a **severe hepatitis**. Autoimmune hepatitis typically occurs in young women, between 20 and 40 years, and often with a family history of autoimmune disorders.

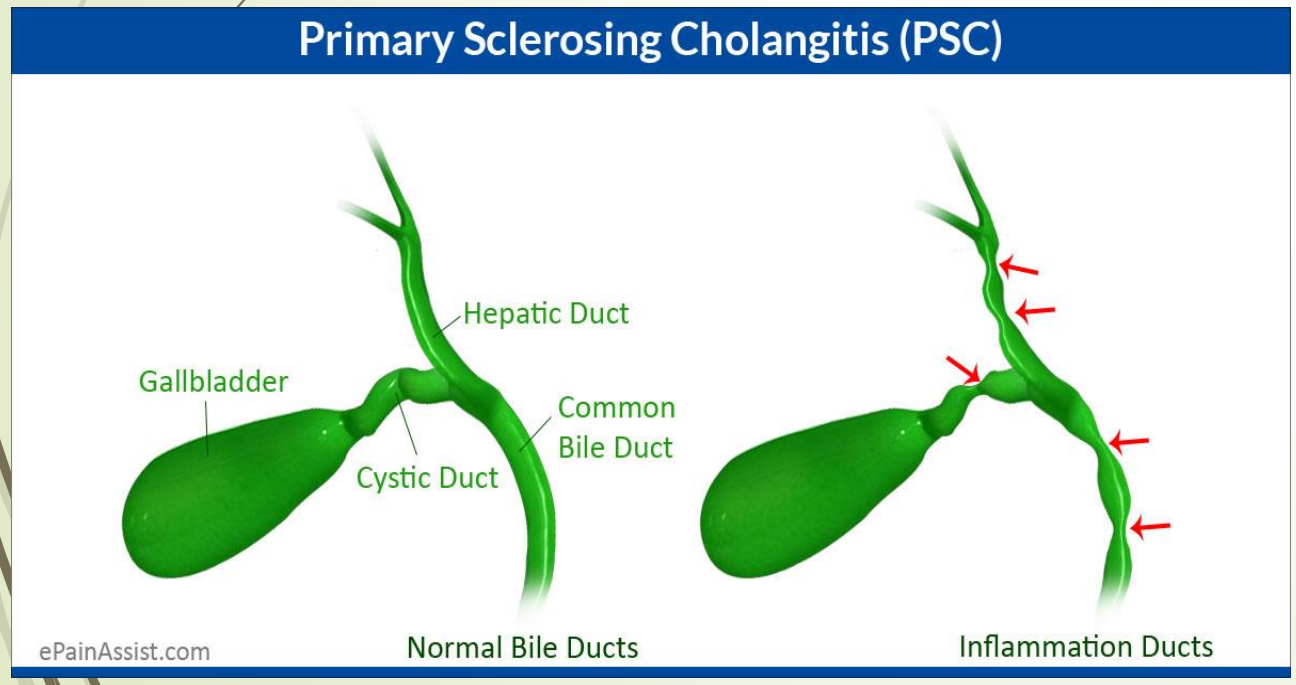
Etiology of Cirrhosis

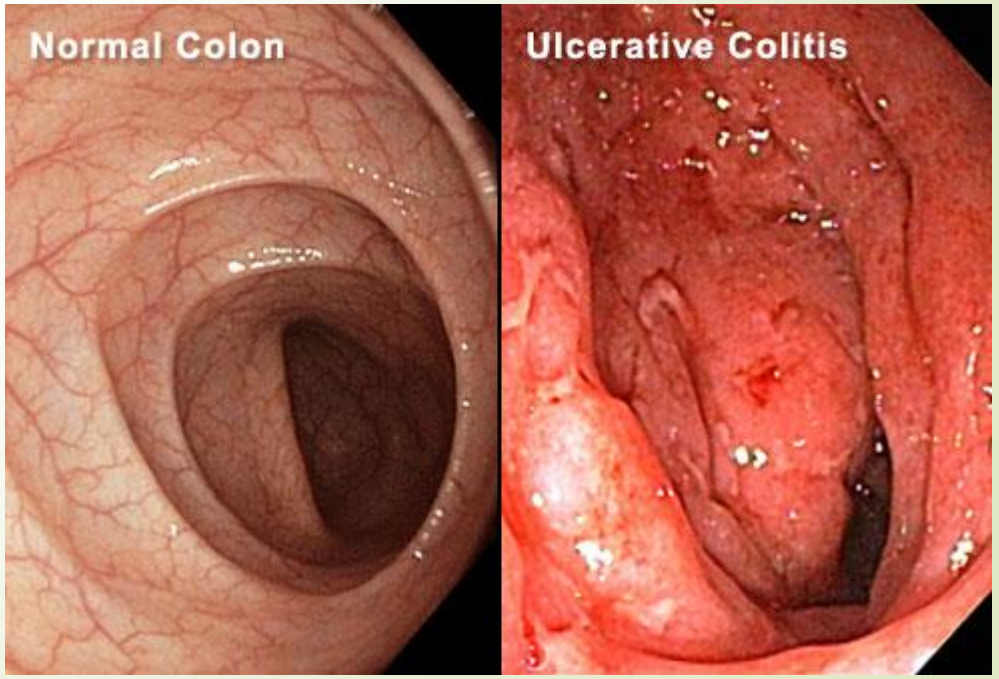
- **Primary biliary cirrhosis**: is an autoimmune disease of the liver which mainly affects middle aged women (95% of cases are female).

- It is characterized by the presence of anti-mitochondrial antibodies that destruct the **interlobular bile ducts** leading to progressive ductopenia, fibrosis and cirrhosis.

Etiology of Cirrhosis

- **Primary sclerosing cholangitis:** is an idiopathic chronic inflammatory disease resulting in biliary strictures, cholestasis and eventually cirrhosis. There is a strong association with inflammatory bowel disease, particularly **ulcerative colitis**.





Etiology of Cirrhosis

- **Metabolic and genetic disorders**: There are various inherited metabolic disorders that can affect the functioning of the liver
  - **Hemochromatosis**
  - **Wilson's disease**
  - **a1-Antitrypsin deficiency**
  - **Glycogen storage disease**
  - **Gilbert's syndrome**

Sign versus Symptom

- **Symptom** is a phenomenon that is experienced by the individual affected by the disease.

- **Sign** is a phenomenon that can be detected by someone other than the individual affected by the disease.

Clinical symptoms of liver disease

- **Weakness**, **fatigue**, and **general malaise** are common but **non-specific** symptoms.
- **Weight loss** and **anorexia** are more commonly seen in **chronic liver disease**.
- **Loss of muscle mass** is a characteristic of **very advanced disease**.
- **Abdominal discomfort** with **liver enlargement** and **ascites** is usually **in more advanced disease**.

Clinical symptoms of liver disease

- **Abdominal pain** is common in **hepatobiliary disease**, frequently localized to the right upper quadrant.

- **Tenderness** (i.e., sensitivity to pain) over the liver is a symptom of **acute hepatitis**, **hepatic abscess** or **hepatic malignancy**.

Clinical symptoms of liver disease

- **Jaundice** is the most striking symptom of liver disease and can present with or without pain, depending on the underlying etiology of disease.

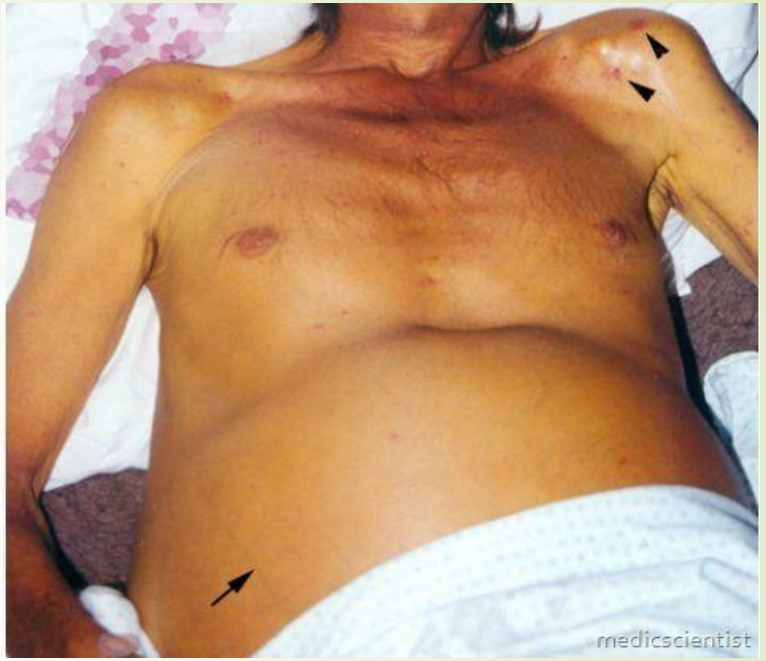
- **Pruritus** can be a distressing symptom in **cholestatic liver disease** and patients usually complain that it is **worse at night**.

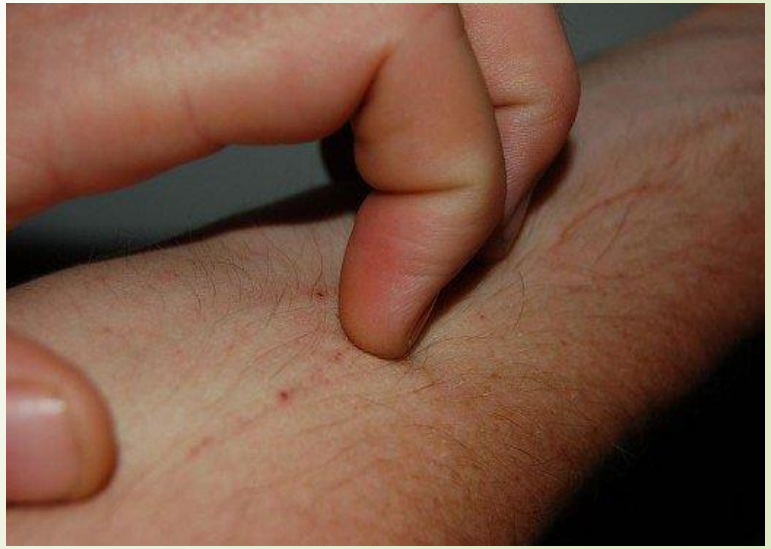
- Patients with acute and chronic liver disease can develop **bleeding** complications because of **defective hepatic synthesis of coagulation factors and low platelet counts**.

Signs of liver disease

Cutaneous signs

- **Hyper pigmentation** result from increased **deposition of melanin**.
- **Scratch marks** on the skin suggest **pruritus** which is common feature of liver disease.



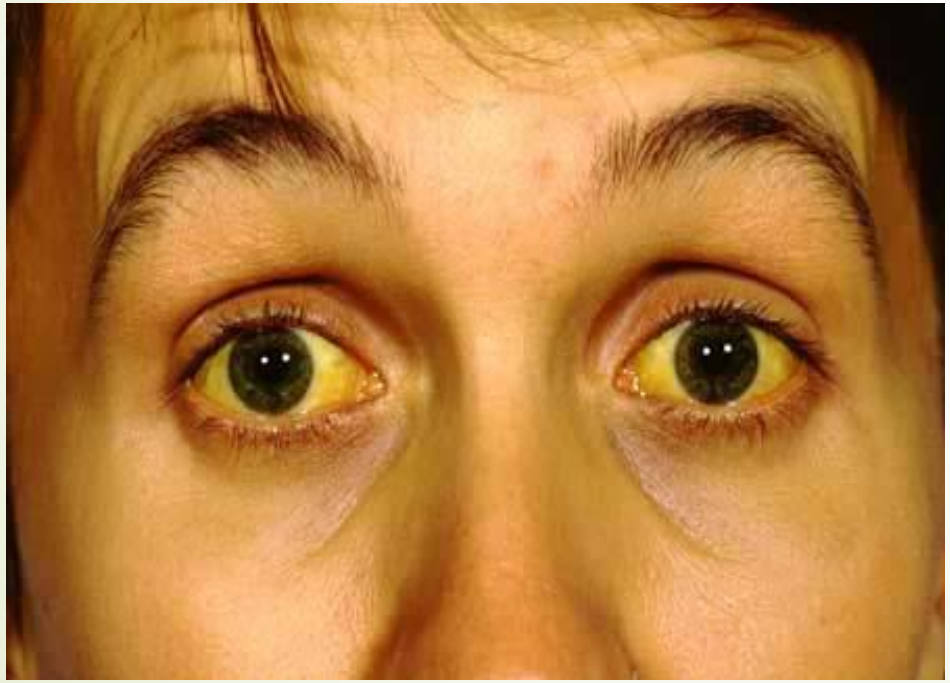


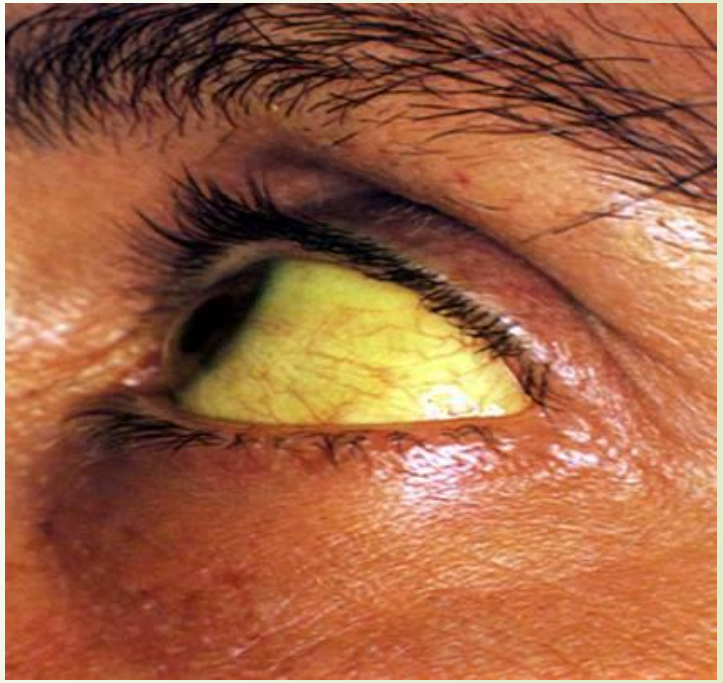
Abdominal signs

- **Abdominal distension**, notably of the flanks, is suggestive of ascites which can develop in both acute (less commonly) and chronic liver disease.
- **Hepatomegaly** is a common finding in **acute liver disease**.
- In cirrhotic patients the liver may be large, but alternatively it may be small and shrunken reflecting end-stage chronic disease.
- **Splenomegaly** in the presence of chronic liver disease is the most important sign of **portal hypertension**.

Jaundice

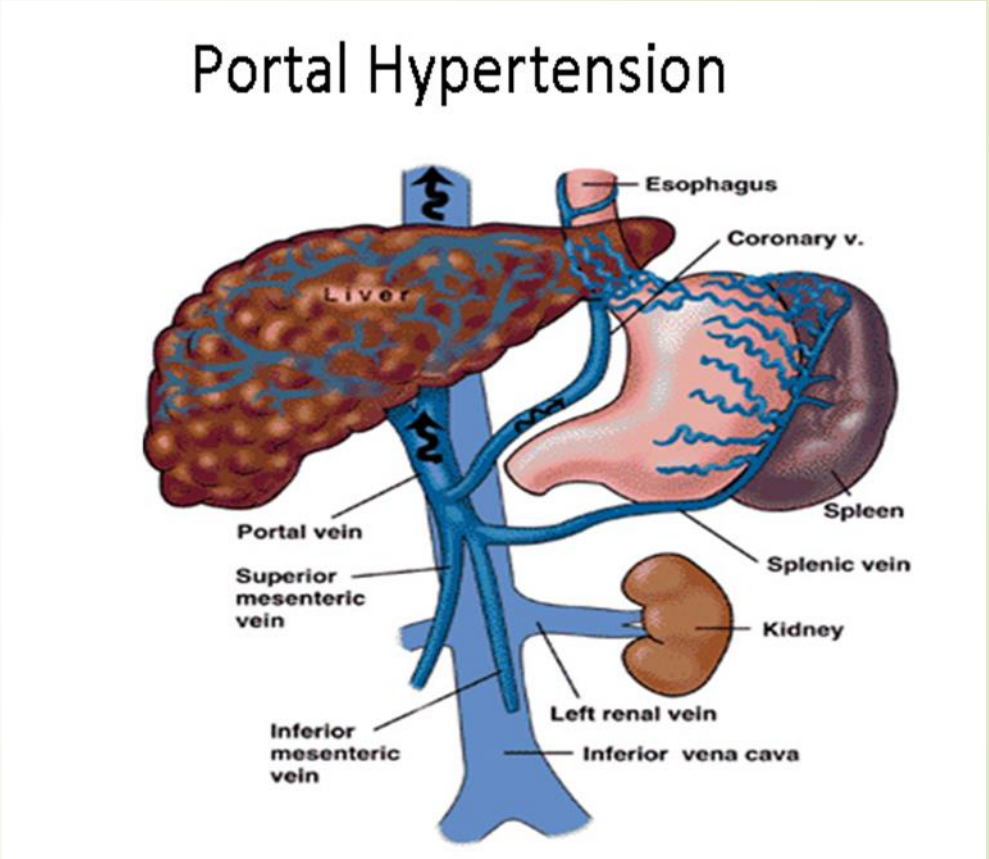
- **Jaundice** is the physical sign regarded as synonymous with **liver disease** and is most easily detected in the **sclerae**.





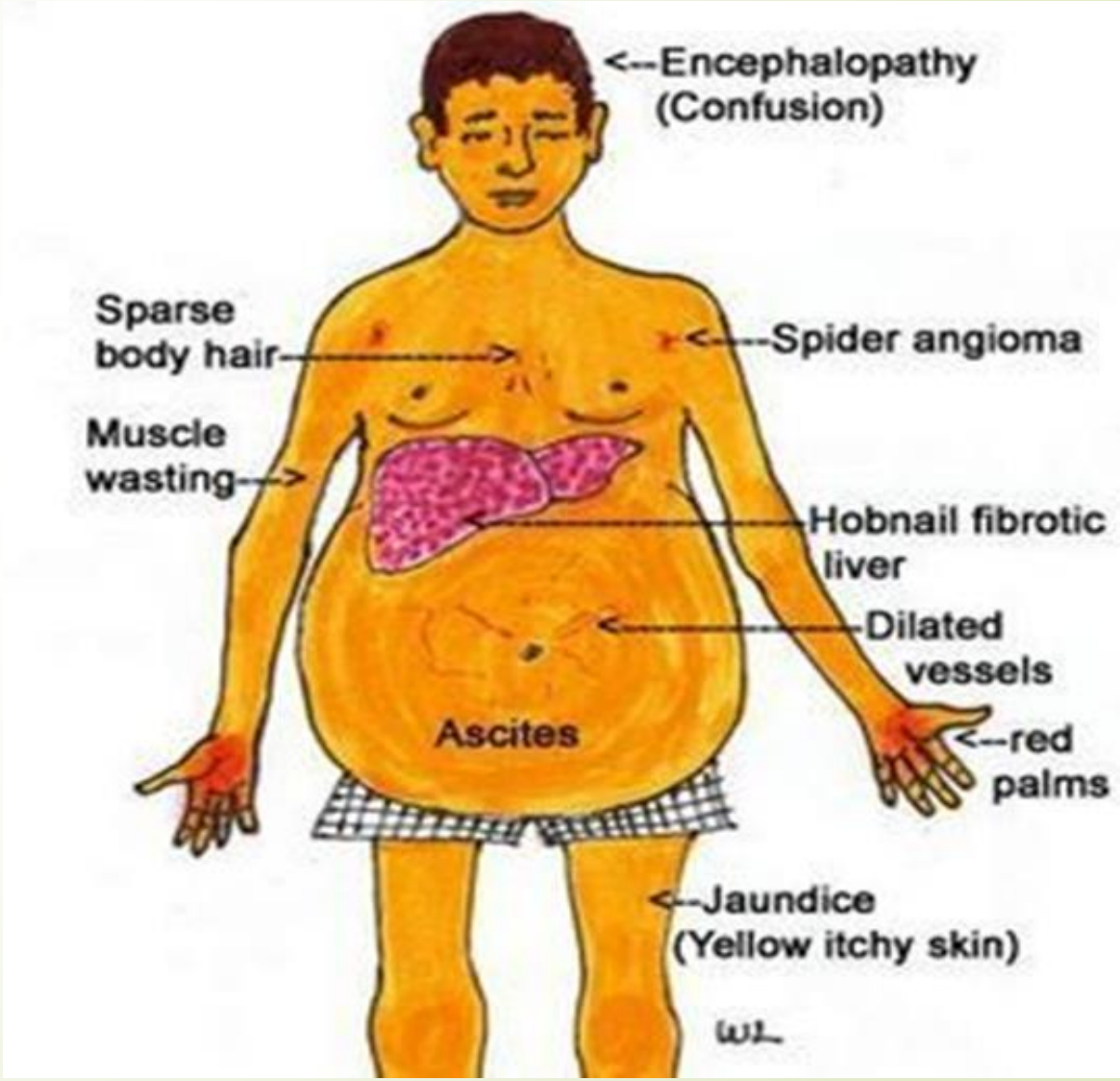
Portal hypertension

- Increased **hepatic resistance to portal flow** due to cirrhosis causes **portal hypertension**.
- The increased pressure in the portal venous system leads to **shunting of blood to the systemic circulation**.



Portal hypertension

- Bypassing of blood from the liver to the systemic circulation lead to:
  - **ascites**
  - **encephalopathy**



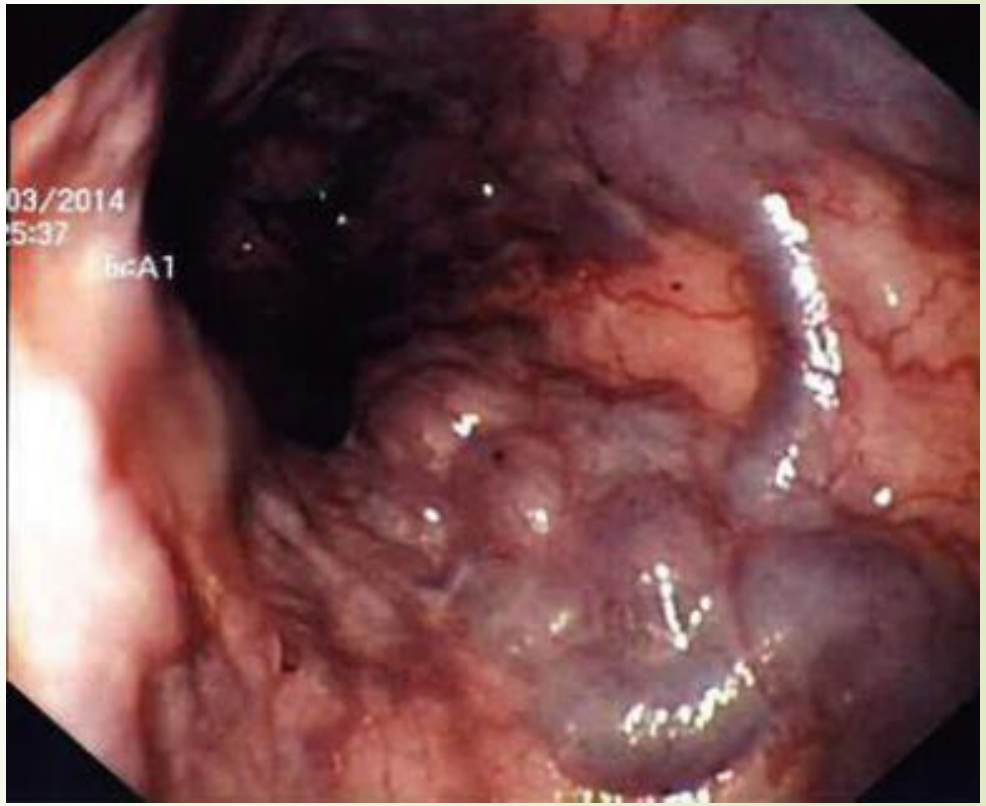
Portal hypertension

- When blood pressure increases in the portal vein system, veins in the **esophagus**, **stomach**, and **rectum** **enlarge to accommodate blocked blood flow through the liver**.

- As the blood pressure in the portal vein system continues to increase, **the walls of these expanded veins become thinner, causing the veins to rupture and bleed**. This is called **variceal bleeding**.

Portal hypertension

- One serious complication of portal hypertension is **variceal bleeding**.



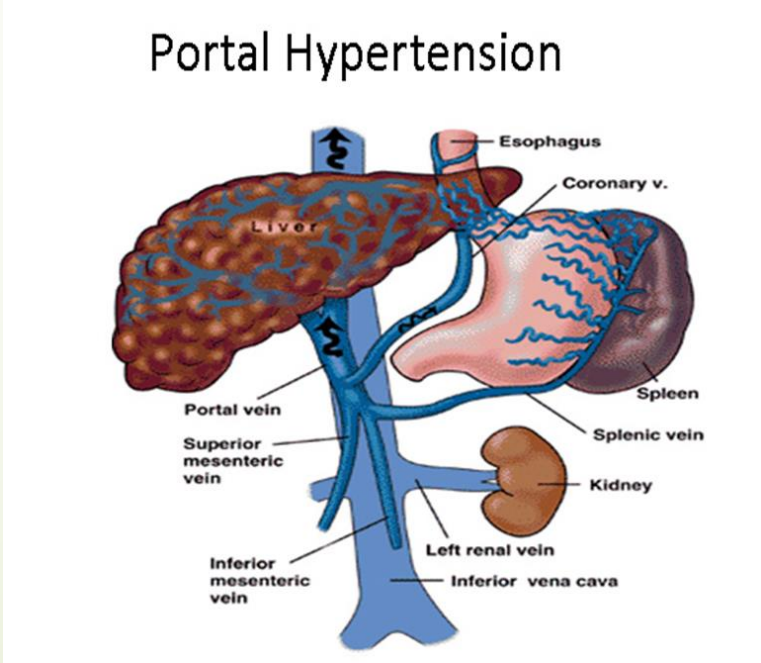
Hepatic encephalopathy

- **Hepatic encephalopathy** is defined as a spectrum of **neuropsychiatric abnormalities** in patients with liver dysfunction.

- It is characterized by
  - **personality changes**
  - **intellectual impairment**
  - **depressed level of consciousness**

Hepatic encephalopathy

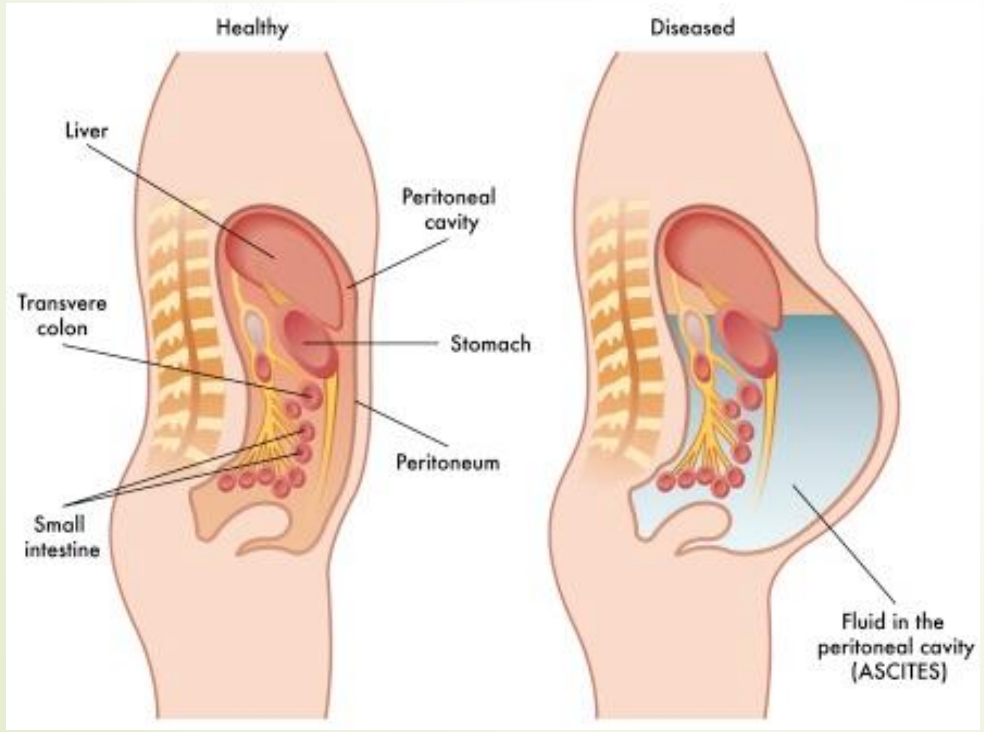
- The development of hepatic encephalopathy is explained, to some extent, by the **effect of neurotoxic substances, which occurs in the setting of cirrhosis** and **portal hypertension**.

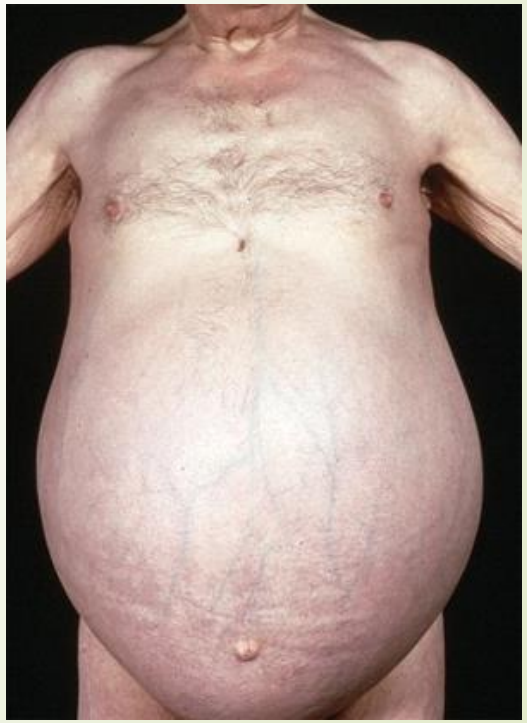


Ascites

- Ascites is a pathologic accumulation of lymph fluid within the peritoneal cavity.

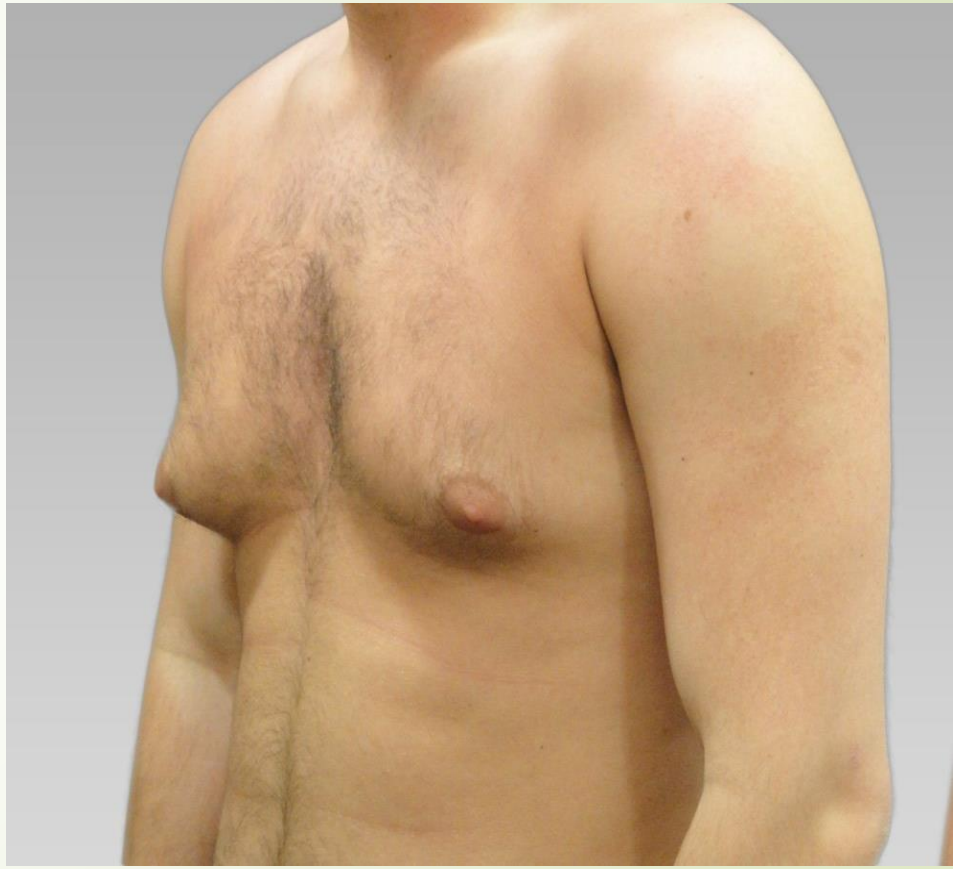
- It is one of the earliest and most common presentations of cirrhosis.





Gynaecomastia

- It tends to be more common in **alcoholic liver disease**.
- Hypogonadism is common in patients with cirrhosis, males may experience **testicular atrophy**.
- It occurs because the **cirrhotic liver cannot metabolize estrogen** leading to **feminization** in **males**.



Women menstruation issues

- Women with chronic liver disease may suffer from
  - **menstrual irregularity**
  - **Amenorrhea**
  - **reduced fertility**

Coagulation defects

- Decreases in the vitamin K-dependent factors (prothrombin; factors VII, IX, and X)
- Decreased synthesis of clotting factors
- Reduction of platelet count (thrombocytopenia)

Bleed tendency

Investigations

- All patients with liver disease must undergo a comprehensive assessment to **identify the underlying etiology**.

- Although **causes** of **acute** and **chronic liver disease** may differ, a similar approach is used to investigate both patient groups.

Biochemical tests

- Liver function tests (LFTs) are
  - Simple
  - inexpensive
  - easy to perform

but usually cannot be used in isolation to make a diagnosis.

Liver function tests

- The liver enzymes usually measured are the
  - **transaminase**
  - **bilirubin**
  - **alkaline phosphatase**
  - **γ-glutamyl transpeptidase**

- **Aspartate transaminase** (AST) and **alanine transaminase** (ALT) are two intracellular enzymes present in hepatocytes which are released into the blood of patients as a consequence of hepatocyte damage.

Liver function tests

- **Extremely high values**, where **transaminases** are recorded in the **thousands**, occur in **acute liver disease**, for example, viral hepatitis or paracetamol overdose.

- **In chronic hepatitis**, serum transaminases are rarely more than five to eight times the normal upper limit.

- Simultaneous elevation of the enzyme **γ-glutamyl transpeptidase** confirms the hepatic origin of an elevated alkaline phosphatase.

Liver function tests

- **Bilirubin** is commonly elevated in hepatocellular pathology and especially in **acute hepatitis** and **end-stage chronic disease**.

- Serum bilirubin can also increase in **Haemolysis.**

Synthetic function capacity

- It is very important in assessing liver disease.

- **Prothrombin time (PT), international normalized ratio (INR)** and other coagulation studies are useful short-term markers of the synthetic function, especially in **acute liver insults** where they reflect the severity of the liver injury.

- **PT** or **INR** are also important indicators of chronic liver disease when combined with **albumin levels**.

Synthetic function capacity

- **Serum albumin** levels reflect liver function over the **previous months** rather than days as with coagulation studies.
- Alternative causes of hypoalbuminaemia need to be considered, especially **proteinuria**.
- Platelets count: Thrombocytopenia is common feature in chronic liver disease found in **30% to 64% of cirrhotic patients**.

Imaging techniques

- **Ultrasound** is a non-invasive, low-risk procedure that is essential in the primary assessment of liver disease as it assesses the **size**, **shape** and **texture** of the liver and screens for dilatation of the **biliary tract**.

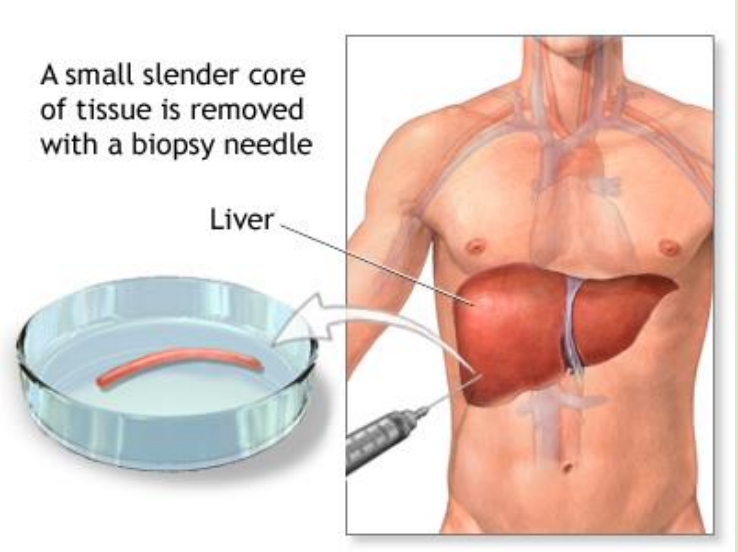
- In patients with **chronic liver disease**, it assesses patency of the **portal vein** and may detect signs of portal hypertension (increased **spleen size, ascites**).

- **Computed tomography (CT)** and **magnetic resonance Imaging (MRI)** scans are regularly used for more precise definition of any abnormalities identified on ultrasound.

Liver biopsy

- Liver biopsy is an invasive procedure with an associated **morbidity** and **mortality**, even though extremely low.

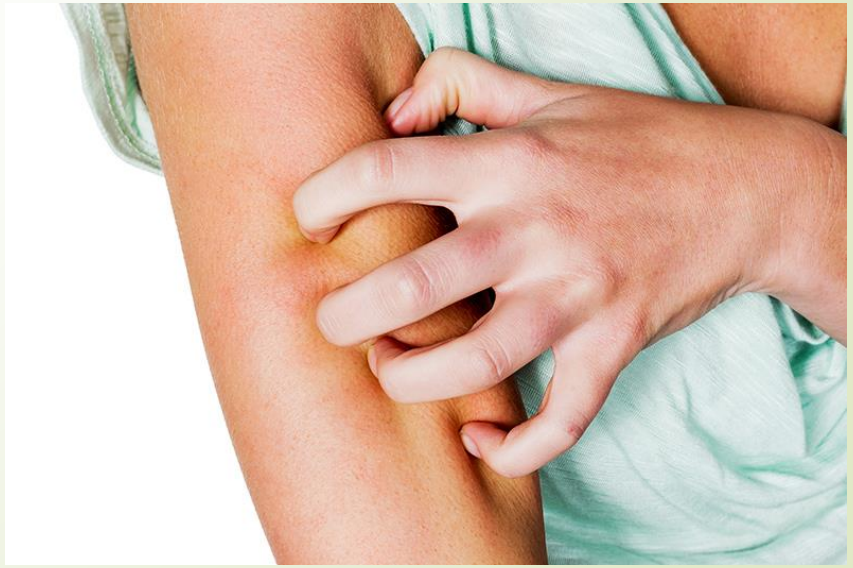
- Nevertheless, it remains the gold standard in establishing a diagnosis and assessing the severity of chronic liver disease.



Management

Pruritus

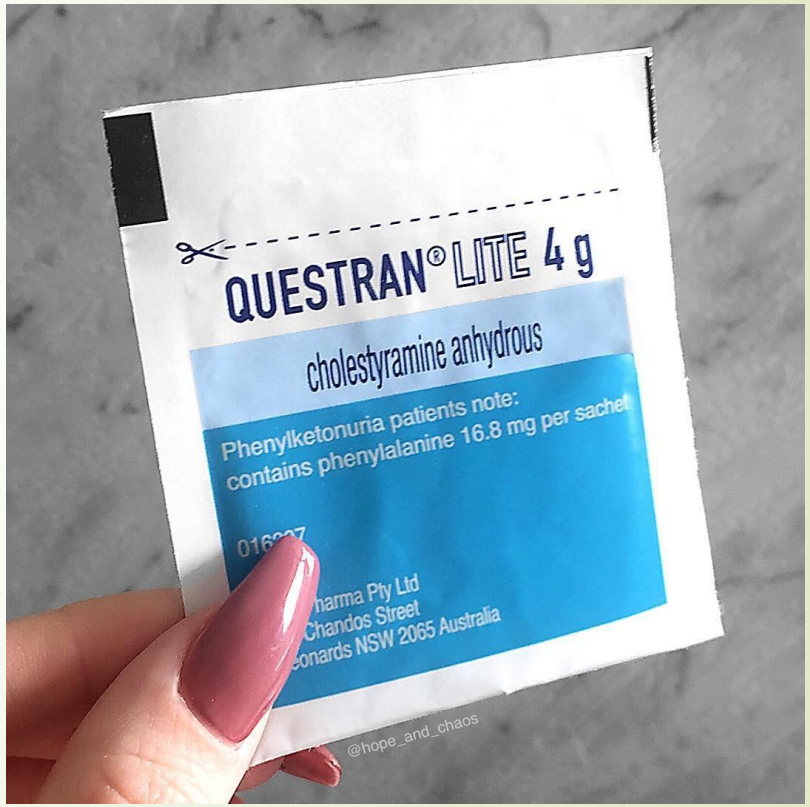
- The deposition of **bile salts within the skin** is considered to be central to its development.
- However, the concentration of bile salts in the skin does not appear to correlate with the intensity of pruritus.
- Management of pruritus is variable.



Pruritus

- **Anion exchange resins** like **Cholestyramine** and **colestipol** act by binding bile acids and preventing their reabsorption.

- These anion exchange resins are the **first line of therapy** in the treatment of pruritus.



Pruritus

- Although frequently used, **antihistamines** are usually **ineffective** in the management of the pruritus caused by cholestasis and **should not be considered first-line therapy**.

- A **non-sedating antihistamine** such as **cetirizine** (10 mg once daily) or **loratadine** (10 mg once daily) is preferred as these avoid precipitating or masking encephalopathy.

Pruritus

- **Sedative antihistamines** such as **chlorphenamine** or **hydroxyzine** they may be useful at night if the severity of pruritus is sufficient to prevent a patient from sleeping.

Pruritus

- **Ursodeoxycholic acid** has been shown to be effective in the treatment of pruritus. However, in about **5% of cases it worsens the pruritus**.

- **Rifampicin** induces hepatic microsomal enzymes, which may benefit some patients, possibly by **improving bile flow**. Its use is restricted by its potential **hepatotoxicity** and **drug interactions** with other agents.

- **Topical therapy** may benefit some patients. **Calamine lotion** or **menthol 2%** cream are standard preparations, but improvement of pruritus with such agents is variable.

Pruritus

- **Opioid antagonists** have been used to treat pruritus because it is believed that endogenous opioids in the central nervous system are potent mediators of itch.

- As a consequence the centrally acting opioid antagonists **naloxone**, **naltrexone** and **nalmefene** are thought to reverse the actions of these endogenous opioids.

Clotting abnormalities

- The majority of clotting factors (with the exception of factor V) are **dependent on vitamin K**.

- Patients with liver disease who develop unbalanced blood clotting should receive **intravenous doses of phytomenadione (vitamin K), usually 10 mg daily for 3 days**.

Clotting abnormalities

- Administration of vitamin K to patients with **significant liver disease does not usually improve the prothrombin time** because the liver is unable to utilize the vitamin to synthesis clotting factors.

- **Oral vitamin K is less effective than the parenteral form** and so, has little or no place in the management of clotting abnormalities and bleeding secondary to liver disease.

Clotting abnormalities

- **Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)** and **anticoagulants** should be avoided in all patients with liver disease because of gastric ulceration and bleeding.

- **NSAIDs** have also been implicated in precipitating **renal dysfunction** and **variceal bleeding** in patients with end-stage liver disease.

- Although **COX-2 inhibitors** may cause a lower incidence of bleeding complications, currently they are avoided in patients with liver disease as their use still poses a risk.

Ascites

- The aim in the treatment of ascites is to mobilize the abnormal collection fluid (intra-abdominal fluid).

- **Salt reduction** combined with **fluid restriction** (approximately **1–1.5 L/day**) are practical measures taken
  - to mobilize fluid
  - To provide weight reduction
  - symptomatic relief

Ascites

- **Aggressive weight reduction** in the absence of peripheral oedema should be **avoided** as it is likely to lead to **intravascular fluid depletion** and **renal failure**.

- Weight loss should not exceed 300–500 g/day in the absence of peripheral oedema and 800–1000 g/day in those with peripheral oedema to prevent renal failure.

Diuretics

- **Spironolactone** is usually used as a **first-line agent in the treatment of ascites**.
- In most instances, a negative sodium balance and loss of ascitic fluid can be achieved with low doses of diuretics.
- Spironolactone can be used alone or in combination with a more potent loop diuretic.

Diuretics

- **Spironolactone** is usually started at **50–100 mg/day**, but this varies, depending on
  - **patient's clinical status**
  - **electrolyte levels**
  - **concomitant drug therapies**

- The addition of a loop diuretic, **furosemide 40 mg/day** enhances the natriuretic activity of spironolactone, and should be used when ascites is severe or when spironolactone alone fails to produce acceptable diuresis.

Diuretics

- The use of more **potent diuretic combinations** may result in **excessive diuresis** which can lead to **renal failure**.
- The **initiation** and **augmentation** of **diuretic therapy** should ideally be carried out in **hospital**.
- This allows strict **urea** and **electrolyte monitoring** to detect impending **hyperkalaemia** and/or **hyponatraemia**, which commonly occur with diuretic therapy.

Diuretics

- Generally, if the serum sodium level **decreases to less than 130 mmol/L** or if creatinine levels rise to greater than **1.5mg/dL** then dose escalation of diuretics should be stopped.

- Diuretic therapy can be complicated by **encephalopathy**, **hypokalaemia**, **hyponatraemia** and **azotemia**.

- **Gynaecomastia** and **muscle cramps** are side effects of diuretic therapy.

Diuretics

- Ascites is considered to be **refractory** or **diuretic resistant** if there is no response with once **daily** doses of **400 mg spironolactone and 160 mg furosemide**.

- Patients on **lower doses of diuretics** are also considered to have **refractory ascites if side effects are a problem**.

Paracentesis

- **Paracentesis** is a procedure to take out fluid that has collected in the belly (peritoneal fluid or ascites).
- The fluid is taken out using a long, thin needle put through the belly.

Paracentesis

- Repeated large volume paracentesis in **combination** with **albumin administration** is the most widely accepted therapy for refractory ascites.
- Patients generally require paracentesis **every 2–4 weeks** and the procedure is often performed in the outpatient setting.
- Paracentesis does not affect the mechanism responsible for ascitic fluid accumulation and so early **recurrence is common**.

Paracentesis

- **Intravenous colloid** replacement or **plasma expanders** are used to prevent adverse effects on the renal and systemic circulation.

- Colloid replacement in the form **albumin** (equivalent to 100 mL of 20% human albumin solution for every 2.5 L of ascitic fluid removed) is a standard regimen.

Spontaneous bacterial peritonitis

- Patients with ascites should be closely observed for **spontaneous bacterial peritonitis** as it **develops in 10–30% of patients** and has a **high mortality**.

- Presenting signs and symptoms can include
  - **Fever and chills (80% of patients)**
  - **changes in mental status**
  - **abdominal tenderness (70% of patients)**
  - **Gastrointestinal bleeding**
  - **Nausea and vomiting**

- It was reported that **around 30% of the cases** are completely **asymptomatic**.

Spontaneous bacterial peritonitis

- A high index of **suspicion** must be maintained when caring for patients with ascites, particularly those with **acute clinical deterioration** like:
  - **Worsening or unexplained encephalopathy**
  - **Diarrhea**
  - **Ascites that does not improve following administration of diuretic medication**
  - **Worsening or new-onset renal failure**
  - **Ileus (a painful obstruction of the ileum or other part of the intestine)**

- However, a leucocyte count of greater than 250 cells/mm^3 is diagnostic of this condition.

Spontaneous bacterial peritonitis

- **Cefotaxime** (2 g, 8 hourly) is effective in 85% of patients with spontaneous bacterial peritonitis and is commonly used as **first-line antimicrobial therapy**.

- Other antibiotic regimens have been used including **co-amoxiclav**, but third-generation cephalosporin are the treatment of choice.

- The quinolone, **norfloxacin (400 mg/day)**, has a role in the prevention of recurrence of spontaneous bacterial peritonitis.

- However, the **emergence of quinolone-resistant bacteria** is a growing problem in the management of spontaneous bacterial peritonitis .

Hepatic encephalopathy

- Therapeutic management is then aimed at reducing the amount of **ammonia** or **nitrogenous products** in the circulatory system.

- **Lactulose**, a non-absorbable disaccharide, it
  - **decreases ammonia production in the gut**.
  - **increases the throughput of bowel contents,** by reducing transit time and also increases soluble nitrogen output in the faeces.
  - is broken down by gastro-intestinal bacteria to form lactic, acetic and formic acids. **The effect of lactulose is to acidify the colonic contents which leads to the ionization of nitrogenous products within the bowel, with a consequent reduction in their absorption from the gastro-intestinal tract.**

Hepatic encephalopathy

- **Lactulose** is commenced in **doses of 30–40 mL/day** and titrated to result in two to three bowel motions each day.

- Patients **unable to take oral** medication or those with **worsening encephalopathy** are treated with **phosphate enemas**.

Phosphate enemas

Hepatic encephalopathy

- Antibiotics such as **metronidazole** or **neomycin** may also be used to **reduce ammonia production** from gastro-intestinal bacteria.
- The use of neomycin has largely been abandoned because of associated toxicity.
- Recent data has supported the use of the **rifaximin**, it is antibiotic used for treatment of encephalopathy.

Drugs commonly used in the management of encephalopathy

Drug	Dose	Comment	Side effects
Lactulose	15–30 mL orally 2–4 times daily	Aim for 2–3 soft stools daily	Bloating, diarrhoea
Metronidazole	400–800 mg orally daily in divided doses	Metabolism impaired in liver disease	Gastro-intestinal disturbance
Neomycin Used less frequently now	2–4 g orally daily in divided doses	Maximum duration of 48 h	Potential for nephro- and ototoxicity
Rifaxamin	550 mg twice daily	Benefit demonstrated over 6 months use	Allergic reactions, gastro-intestinal disturbance May permit overgrowth *Clostridium difficile*

Esophageal varices

- All patients with cirrhosis and portal hypertension should be considered for **endoscopic screening**, and patients with large varices should receive primary prophylaxis with **β- adrenergic blockers**.

- Non-selective β-blockers, such as **propranolol**, are the medication of choice for
  - **primary prophylaxis against variceal bleeding**
  - **Prevent variceal rebleeding**

Esophageal varices

- The mechanism of action of β-blockers is complex, but they **reduce portal hypertension** by causing splanchnic vasoconstriction and reduced portal blood flow.

- **Propranolol** initiate with a dose of 10mg thrice daily, then dose should titrated to reduce resting heart by 25% (i.e., 55-60 beats/min).

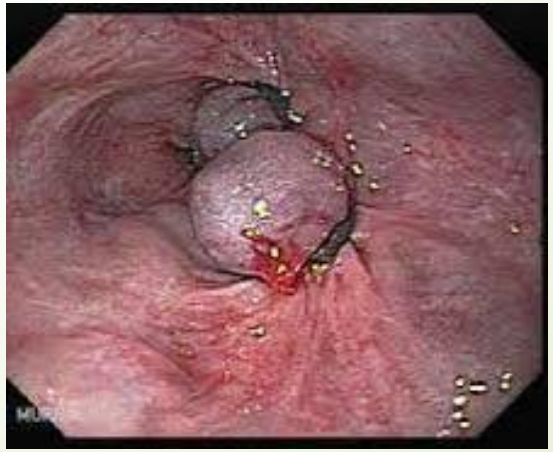
- **At higher doses** β-blockers can have a more marked negative effect on cardiac output and so must be titrated accordingly.

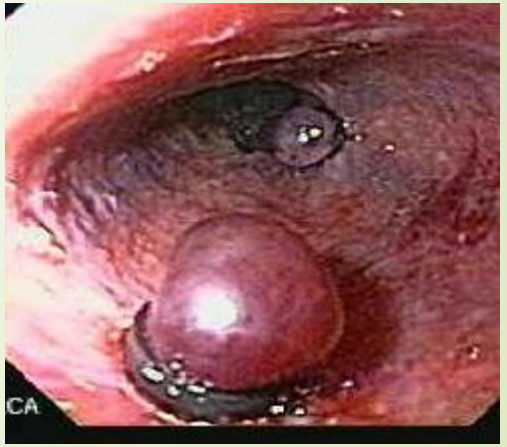
Esophageal varices

Endoscopic management:

- Variceal band ligation uses prestretched rubber bands applied to the base of a varix which has been sucked into the banding chamber attached to the front of an endoscope.

- Variceal band ligation controls bleeding in approximately 90% of cases. It is associated with few side effects.





Esophageal varices

- **Endoscopic band ligation** is performed at regular intervals **(1–2 weeks)** as part of an eradication program to eliminate the varices. Once varices have been eradicated, endoscopic follow-up can be performed less frequently **(3 monthly)** for the first year, then **twice yearly** thereafter.

Esophageal varices

- Several pharmacological agents are available for the **emergency control of variceal bleeding**.

- Most act by lowering portal venous pressure. They are generally used to control bleeding in addition to emergency endoscopic techniques.

- **Vasopressin** was the first vasoconstrictor used to reduce portal pressure in patients with actively bleeding varices. However, its associated systemic vasoconstrictive adverse effects limited its use.

Esophageal varices

- The synthetic vasopressin analogue, **Terlipressin**, is highly effective in controlling bleeding and in reducing mortality.
- **Terlipressin** can be administered in **bolus doses every 4–6 h** and has a **longer biological activity** and a **more favorable side effect profile**.
- Once a diagnosis of variceal bleeding has been established, a vasoactive drug infusion (usually **terlipressin**) should be started **without further delay and continued for 2–5 days**.

Esophageal varices

- **Somatostatin** and the **Somatostatin analogue, octreotide**, are reported to reduce portal pressure. Although they are reported to cause less adverse effects on the systemic circulation, **terlipressin** remains the agent of choice.

Drugs used in the treatment of acute bleeding varices

Drug	Dosage and administration
Terlipressin	1–2 mg bolus 4–6 hourly for 48 h
Octreotide	50 µcg/h i.v. infusion for 48 h or longer if patient rebleeds

Are you happy?