Liver Cirrhosis

BY:
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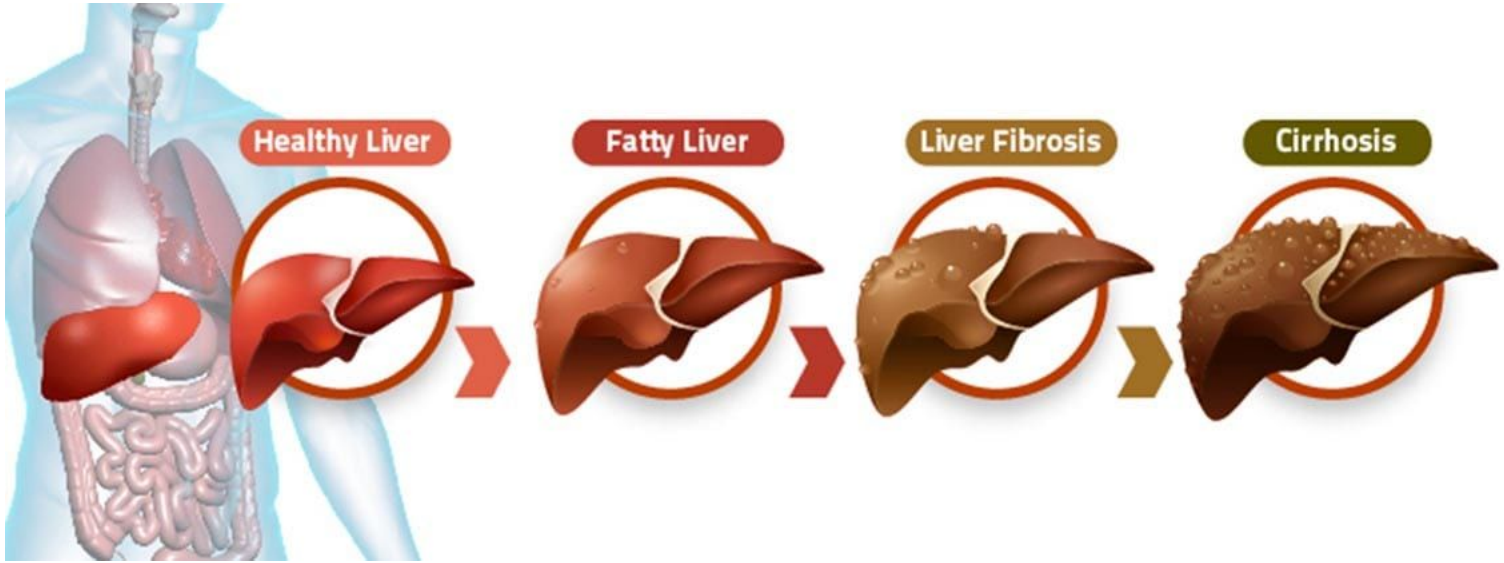
LA-2-CO-171(2)


Healthy Liver
Fatty Liver
Liver Fibrosis
Cirrhosis

“

Liver cirrhosis is a chronic liver disease accompanied by irreversible replacement of parenchymal liver tissue by fibrous connective tissue.

Etiology

- Alcohol
- Hepatitis B can cause liver inflammation and damage that can lead to cirrhosis.
- Hepatitis C occurs by sexual intercourse or exposure to infected blood or blood products
- Hepatitis D can also cause cirrhosis. It's often seen in people who already have hepatitis B.
- Autoimmune hepatitis causes inflammation that can lead to cirrhosis.

- Damage to the bile ducts, which function to drain bile: One example of such a condition is primary biliary cholangitis.
- Disorders that affect the body's ability to handle iron and copper: Two examples are hemochromatosis and Wilson's disease.
- Medications, including prescription and over-the-counter drugs like acetaminophen, some antibiotics, and some antidepressants, can lead to cirrhosis.

Classification

1

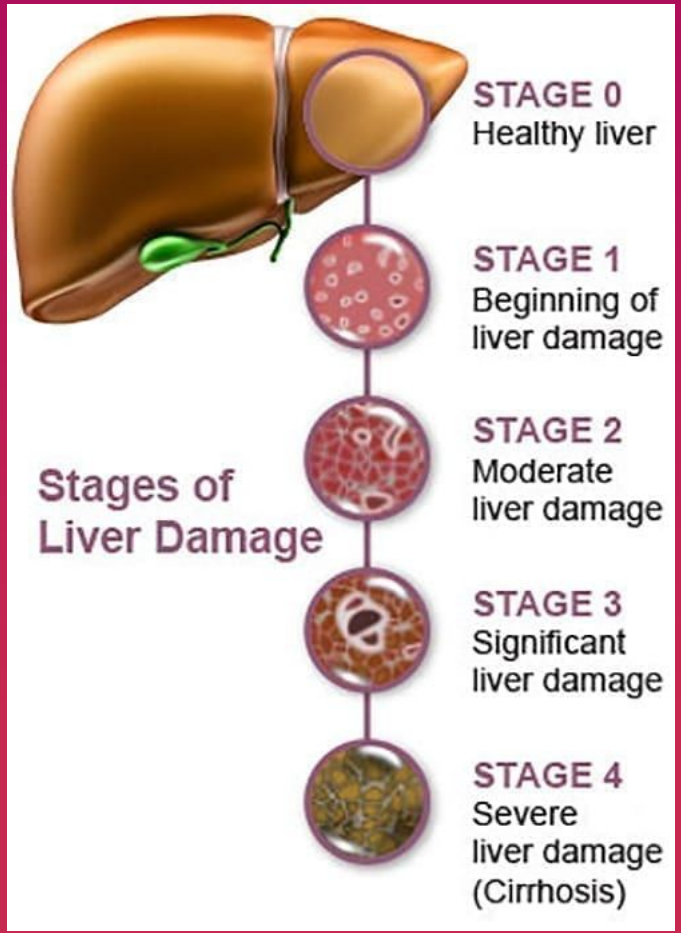
- According to etiology:
  - Postinfectious cirrhosis- viruses, parasites, syphilis, bacterial infection of biliary tract
  - Toxic and toxic allergic cirrhosis- alcohol, drugs, hepatotoxic poisons
  - Metabolic and nutritional cirrhosis- deficiency of proteins, vitamins, lipotropic factors, Wilson's disease (impaired copper metabolism)
  - Primary biliary cirrhosis- due to destructive cholangitis or cholangiolitis
  - Secondary biliary cirrhosis- due to obstruction of the biliary tract or infectious (bacterial) cholangitis
  - Circulatory- as a result of chronic venous congestion

- According to macroscopic appearance:
  - Micronodular cirrhosis
  - Macronodular cirrhosis
- According to microscopic appearance:
  - Monolobular cirrhosis
  - Multilobular cirrhosis
- According to morphogenesis:
  - Portal
  - Post necrotic
  - mixed

- According to course:
  - Active
  - Inactive

Pathogenesis

2


Stages of
Liver Damage
STAGE 0
Healthy liver
STAGE 1
Beginning of
liver damage
STAGE 2
Moderate
liver damage
STAGE 3
Significant
liver damage
STAGE 4
Severe
liver damage
(Cirrhosis)

- Irrespective of the aetiology, cirrhosis in general is initiated by hepatocellular necrosis
- Replacement of BM collagen type iv and vi by fibrillary collagen type I and iii
- This lead to capillarization with quantitative and qualitative ECM change

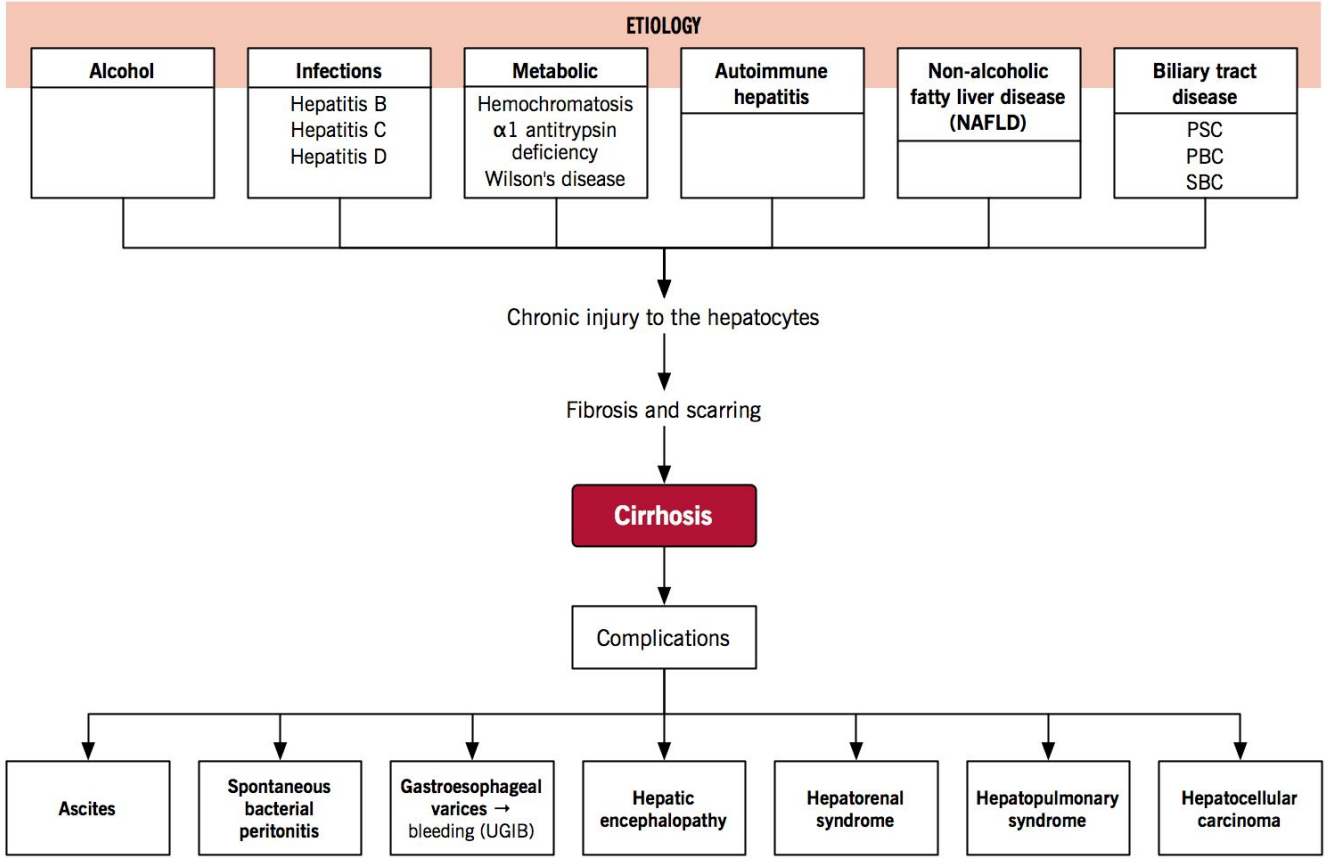
- ECM regulates cellular activity and availability of growth factors
  - Decorin and biglycan binds TGF-B
  - Fibronectin and laminin binds TNF-alpha
  - Collagen binds PDGF, HGF, IL-2
- Binding of the survival factors to ECM prevents apoptosis in damage liver and proteolysis
- ECM can modulate the activation of & proliferation of HSC, angiogenesis GF & MMP

- HSC activation represents a critical event in the fibrosis
- This cell become the primary source of ECM in liver upon injury
- This is modulated by immune signaling that is influence by genetic and environmental factors

- Sources of ECM
  - HSC
  - Bone marrow derive cells
  - Epithelial mesenchymal transition
  - Portal fibroblast

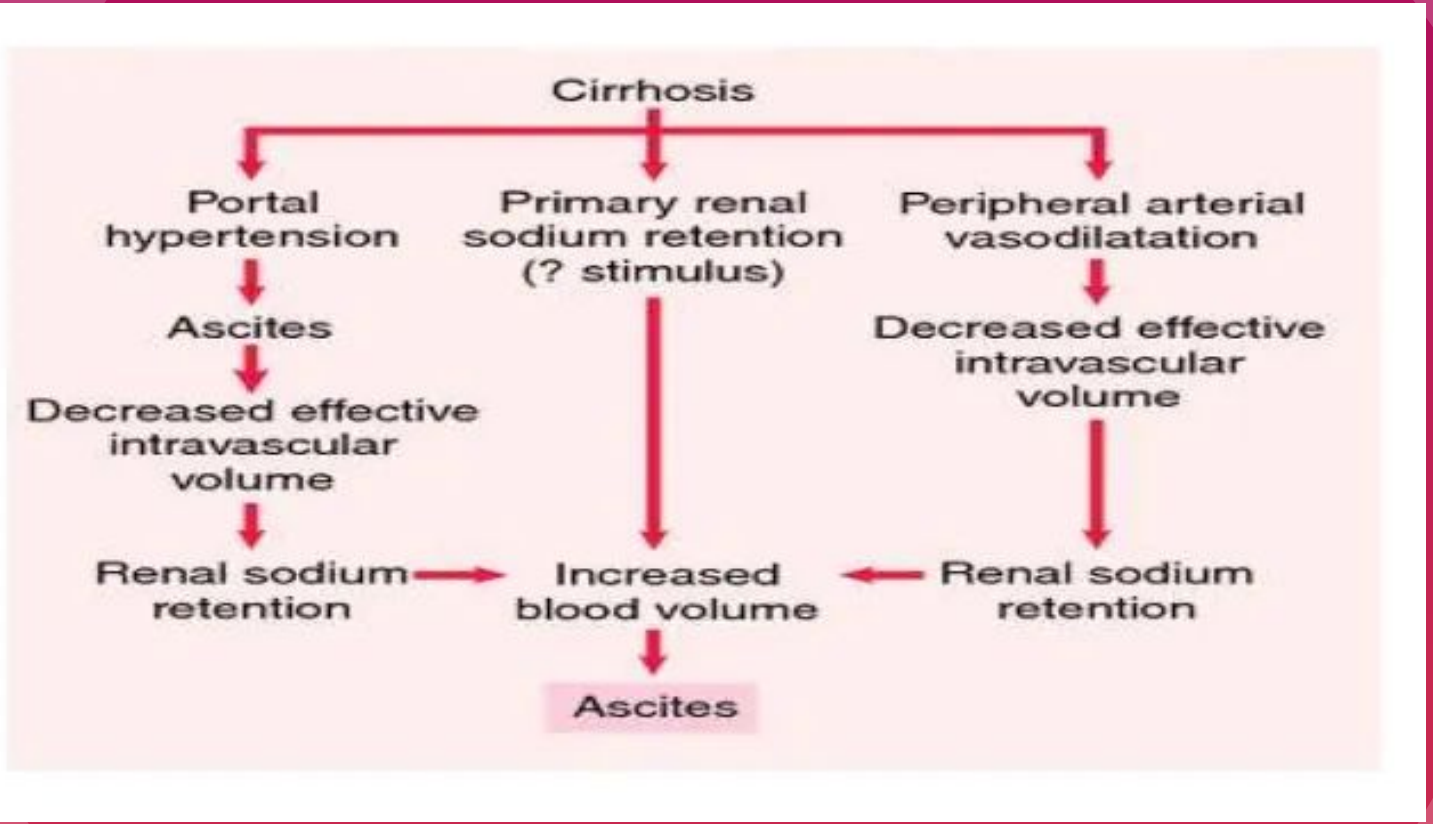
CIRRHOSIS | Etiology and complications of cirrhosis

Sultan Chaudhry



CYTOKINES AND SIGNALING PATHWAYS

- Inflammatory cytokines play a key role in fibrosis, given that persistent inflammation precedes fibrosis.
- Following liver injury, several cell types can secrete inflammatory cytokines;
- Cell types include; KCs, hepatocytes, HSCs, natural killer (NK)cells, lymphocytes, and dendritic cells.
- Ligand + receptor = transduction of extracellular signals into the cell =modulation of changes in gene expression.
- Common form of ligand-receptor interaction=dimerization/trimerization of receptor molecules
    - Receptors with intrinsic tyrosine kinase
    - Receptors lacking intrinsic tyrosine kinase activity .


Cirrhosis
Portal hypertension
Primary renal sodium retention (? stimulus)
Peripheral arterial vasodilatation
Ascites
Decreased effective intravascular volume
Decreased effective intravascular volume
Renal sodium retention
Increased blood volume
Renal sodium retention
Ascites

Systemic Syndromes

Clinical entity	cause/mechanism
Portal hypertension	Architectural and functional changes in liver resulting in increased resistance to portal flow leading to portosystemic collaterals, splanchnic vasodilation, expanded plasma volume and arterial underfilling
Portopulmonary hypertension	Vasoactive substances not filtered by the damaged liver causing pulmonary artery vasoconstriction, remodeling of vessels and in situ thrombosis resulting in increasing pulmonary vasculature resistance and ultimately right heart failure
Hepatopulmonary syndrome	Intrapulmonary vascular dilatation due to nitric oxide (NO) or arteriovenous communication (with a predominance at lung bases) causes ventilation/perfusion mismatch and/or shunting which worsens when upright due to dependent pooling of blood at bases
Hepatorenal syndrome	Renal failure caused by intense vasoconstriction of the renal circulation as a consequence of extreme underfilling of arterial circulation due to splanchnic vasodilation (due to high NO levels) and dysregulation of vasocoactive systems in the setting of advanced liver disease

Clinical Features

3

The symptoms of cirrhosis occur because the liver is unable to purify the blood, break down toxins, produce clotting proteins, and help with absorption of fats and fat-soluble vitamins. Often, there are no symptoms until the disorder has progressed. Some of the symptoms include:

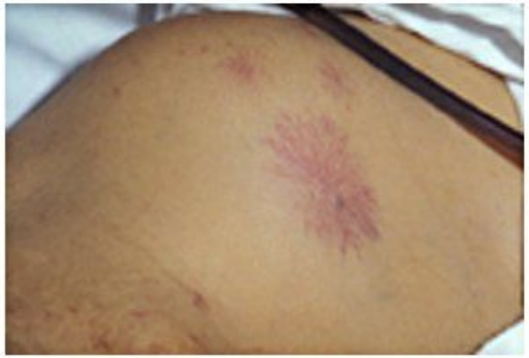
- decreased appetite
- nose bleeds
- jaundice (yellow discoloration)
- small spider-shaped veins underneath the skin
- weight loss
- anorexia
- itchy skin
- weakness

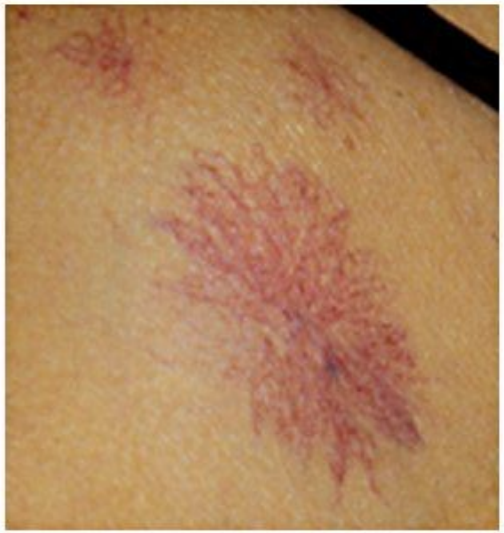
- More serious symptoms include:
- confusion and difficulty thinking clearly
- abdominal swelling (ascites)
- swelling of the legs (edema)
- impotence
- gynecomastia (when males start to develop breast tissue)

Liver dysfunction

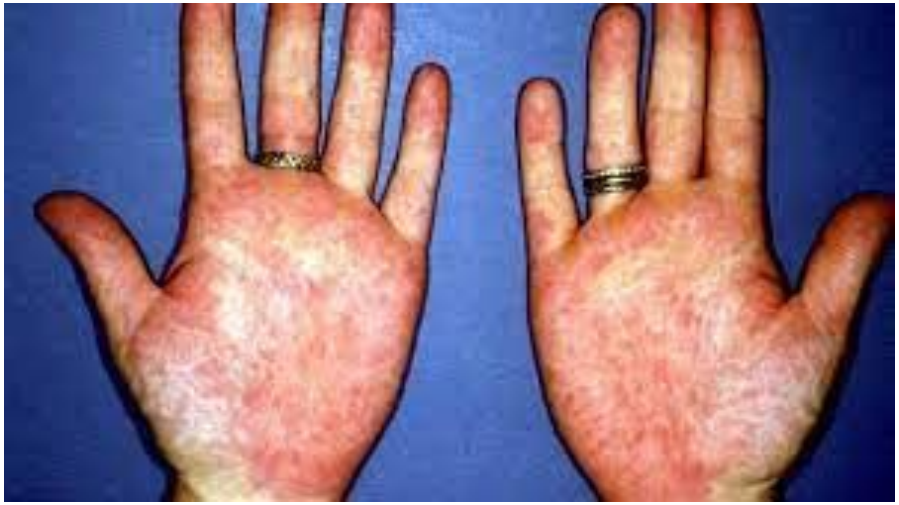
The following features are a direct consequence of liver cells not functioning.

- Spider angiomata or spider nevi are vascular lesions consisting of a central arteriole surrounded by many smaller vessels (hence the name "spider") and occur due to an increase in estradiol. One study found that spider angiomata occur in about 1/3 of cases.
- Palmar erythema is a reddening of palms at the thenar and hypothenar eminences seen in about 23% of cirrhosis cases as a result of increased estrogen.
- Gynecomastia, or benign increase in breast size in men, is caused by increased estradiol and can occur in up to 2/3 of cases. This is different from increase in breast fat in overweight people. A swollen scrotum may also be evident.
- Hypogonadism, a decrease in male sex hormones may manifest as impotence, infertility, loss of sexual drive, and testicular atrophy, and can result from primary gonadal injury or suppression of hypothalamic/pituitary function. Hypogonadism is associated with cirrhosis due to alcoholism or iron overload.
- Liver size can be enlarged, normal, or shrunken in people with cirrhosis.
- Ascites, accumulation of fluid in the peritoneal cavity in the abdomen, gives rise to

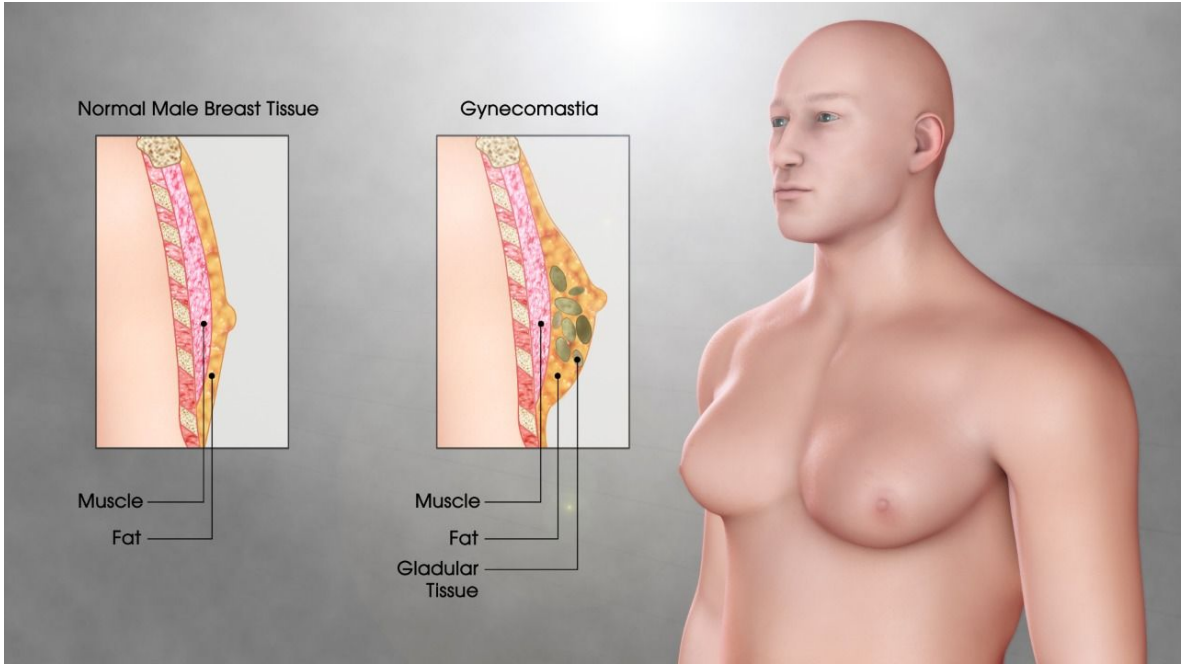


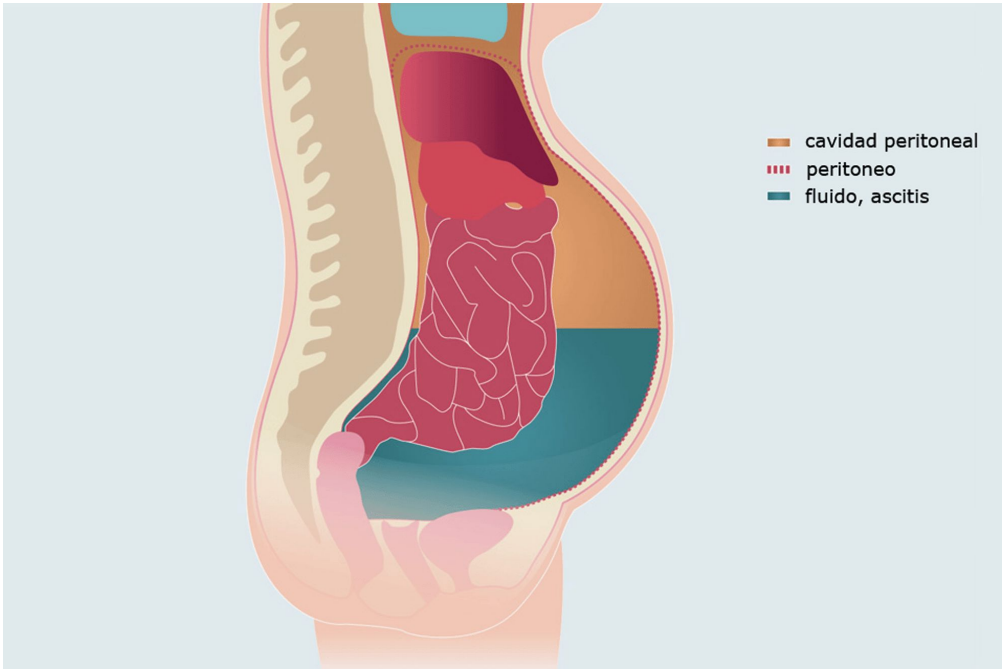


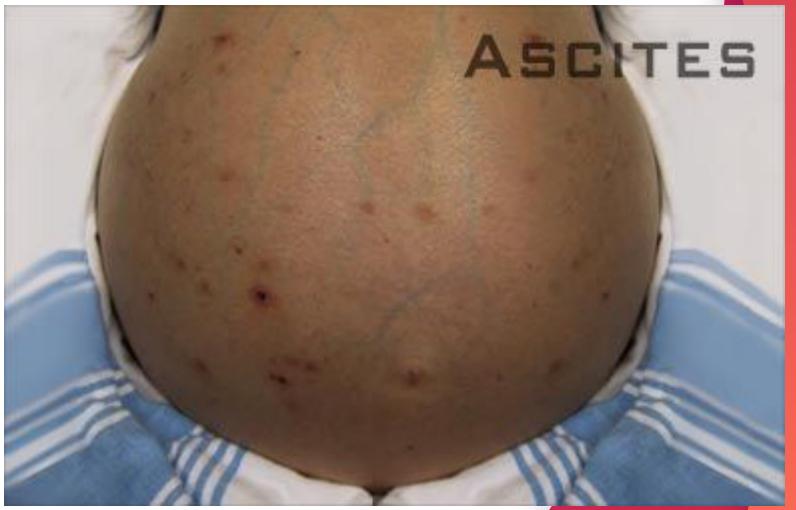
Spider angiomata



Palmnar Erythema

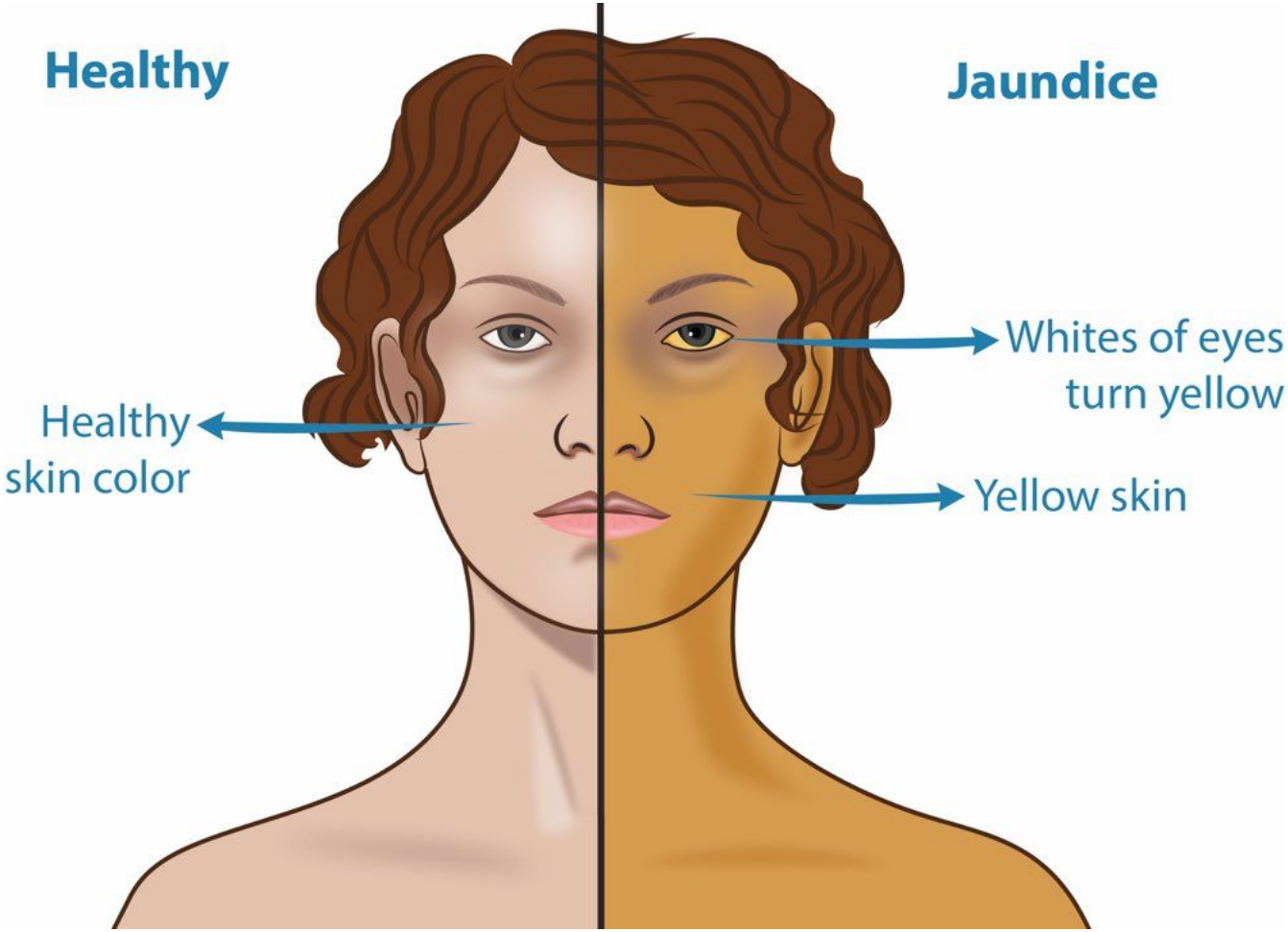

Normal Male Breast Tissue
Muscle
Fat
Gynecomastia
Muscle
Fat
Gladular
Tissue


cavidad peritoneal
peritoneo
fluido, ascitis


ASCITES

Epitaxis

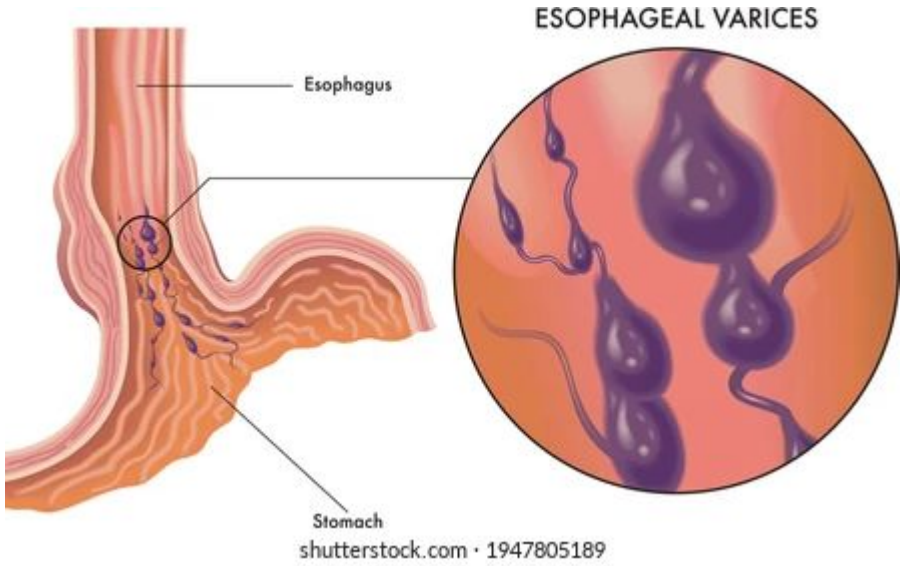
Jaundice


Healthy
Jaundice
Whites of eyes turn yellow
Healthy skin color
Yellow skin

Portal hypertension

Liver cirrhosis increases resistance to blood flow and leads to higher pressure in the portal venous system, resulting in portal hypertension. Effects of portal hypertension include:

- An enlarged spleen is found in 35% to 50% of cases.
- Esophageal varices result from collateral portal blood flow through vessels in the stomach and esophagus (a process called portacaval anastomosis). When these blood vessels become enlarged, they are called varices and are more likely to rupture. Variceal rupture often leads to severe bleeding, which can prove fatal.
- Caput medusae are dilated paraumbilical collateral veins due to portal hypertension. Blood from the portal venous system may be shunted through the paraumbilical veins and ultimately to the abdominal wall veins, manifesting as a pattern that may resemble the head of Medusa.
- Cruveilhier-Baumgarten bruit is a venous hum heard in the epigastric region (on examination by stethoscope) due to collateral connections forming between the portal system and the paraumbilical veins as a result of portal hypertension.


ESOPHAGEAL VARICES
Esophagus
Stomach
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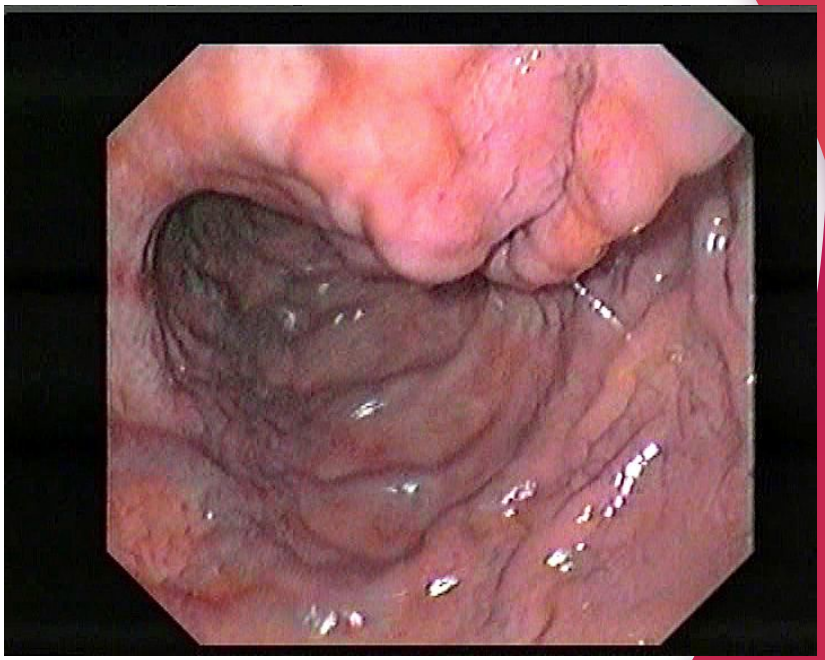
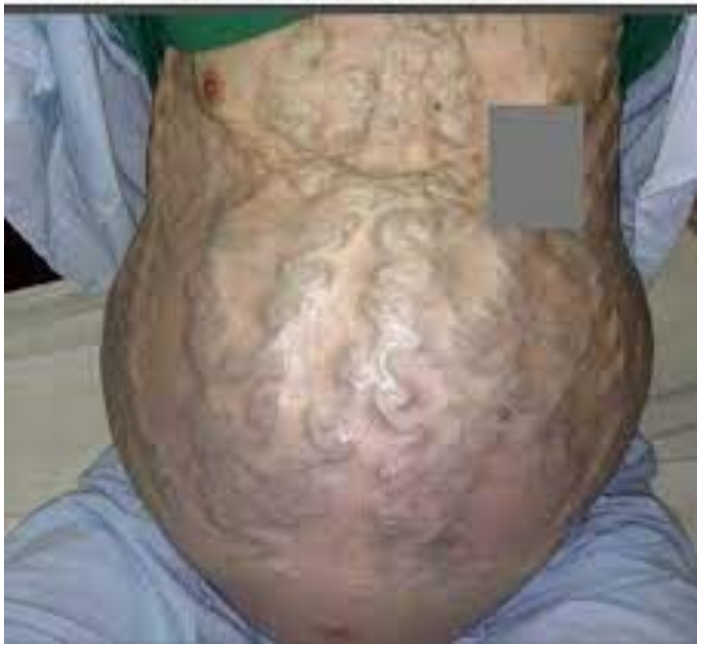


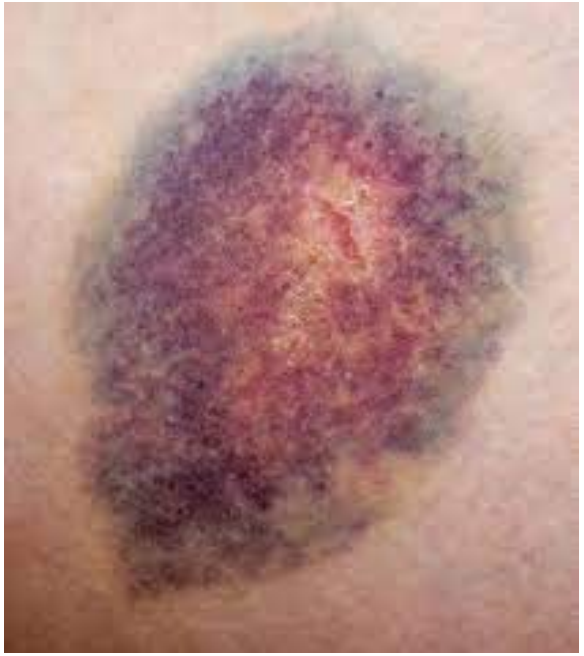
CAPUT MEDUSAE



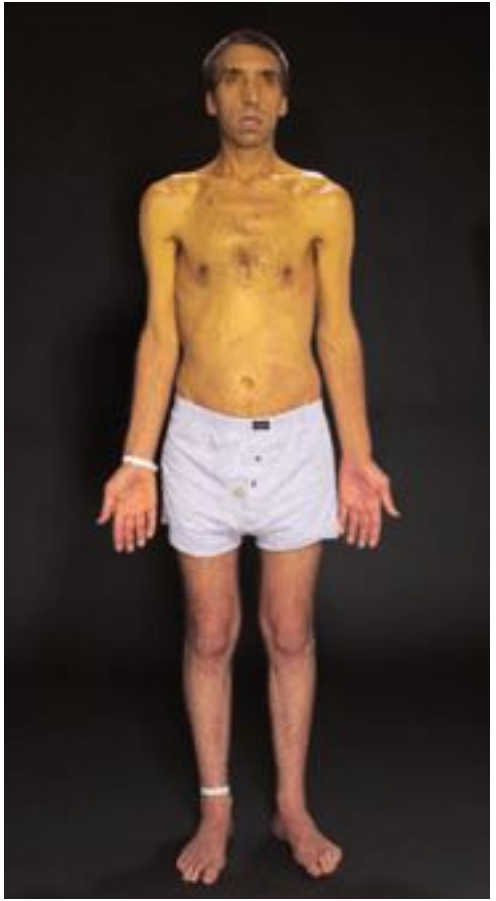
Advanced disease

As the disease progresses, complications may develop. In some people, these may be the first signs of the disease.

- Bruising and bleeding resulting from decreased production of clotting factors.
- Hepatic encephalopathy (HE) – occurs when ammonia and related substances build up in the blood and affect brain function when they are not cleared from the blood by the liver. This may result in neglect of personal appearance, unresponsiveness, forgetfulness, trouble concentrating, changes in sleep habits or psychosis. One classic physical exam findings is asterixis, bilateral asynchronous flapping of outstretched, dorsiflexed hands. Fetor hepaticus is a musty breath odor resulting from increased dimethyl sulfide and is a feature of HE.
- Sensitivity to medication caused by decreased metabolism of the active compounds.
- Acute kidney injury (particularly hepatorenal syndrome).



Bruising



Cachexic patient with jaundice

Lab findings

- The following findings are typical in cirrhosis:
- Thrombocytopenia – typically multifactorial. Due to alcoholic marrow suppression, sepsis, lack of folate, platelet sequestering in the spleen as well as decreased thrombopoietin. However, this rarely results in a platelet count < 50 000/mL.
- Aminotransferases – AST and ALT are moderately elevated, with AST > ALT. However, normal aminotransferase levels do not preclude cirrhosis.
- Alkaline phosphatase – slightly elevated but less than 2–3 times the upper limit of normal.
- Gamma-glutamyl transferase – correlates with AP levels. Typically much higher in chronic liver disease from alcohol.
- Bilirubin – levels normal when compensated but may elevate as cirrhosis progresses.

- Prothrombin time – increases, since the liver synthesizes clotting factors.
- Globulins – increased due to shunting of bacterial antigens away from the liver to lymphoid tissue.
- Serum sodium – hyponatremia due to inability to excrete free water resulting from high levels of ADH and aldosterone.
- Leukopenia and neutropenia – due to splenomegaly with splenic margination.
- Coagulation defects – the liver produces most of the coagulation factors and thus coagulopathy correlates with worsening liver disease.
- Glucagon – increased in cirrhosis
- Vasoactive intestinal peptide – increased as blood is shunted in the intestinal system because of portal hypertension
- Vasodilators – increased (such as nitric oxide and carbon monoxide) reducing afterload with compensatory increase in cardiac output, mixed venous oxygen saturation

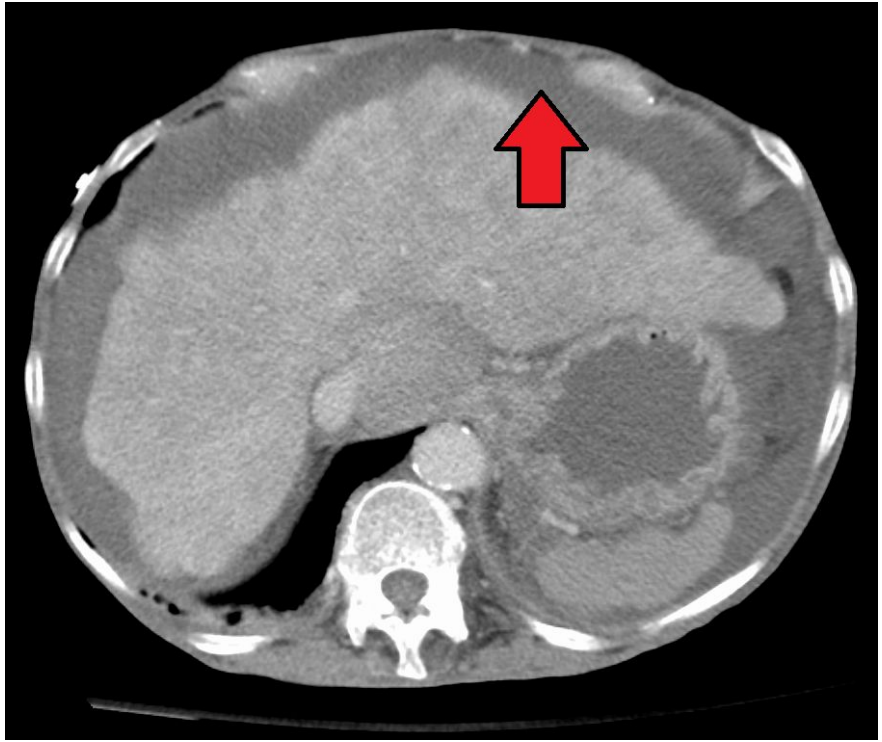
Other laboratory studies performed in newly diagnosed cirrhosis may include:

- Serology for hepatitis viruses, autoantibodies (ANA, anti-smooth muscle, anti-mitochondria, anti-LKM)
- Ferritin and transferrin saturation: markers of iron overload as in hemochromatosis, copper and ceruloplasmin: markers of copper overload as in Wilson's disease
- Immunoglobulin levels (IgG, IgM, IgA) – these immunoglobins are non-specific but may help in distinguishing various causes
- Cholesterol and glucose
- Alpha 1-antitrypsin

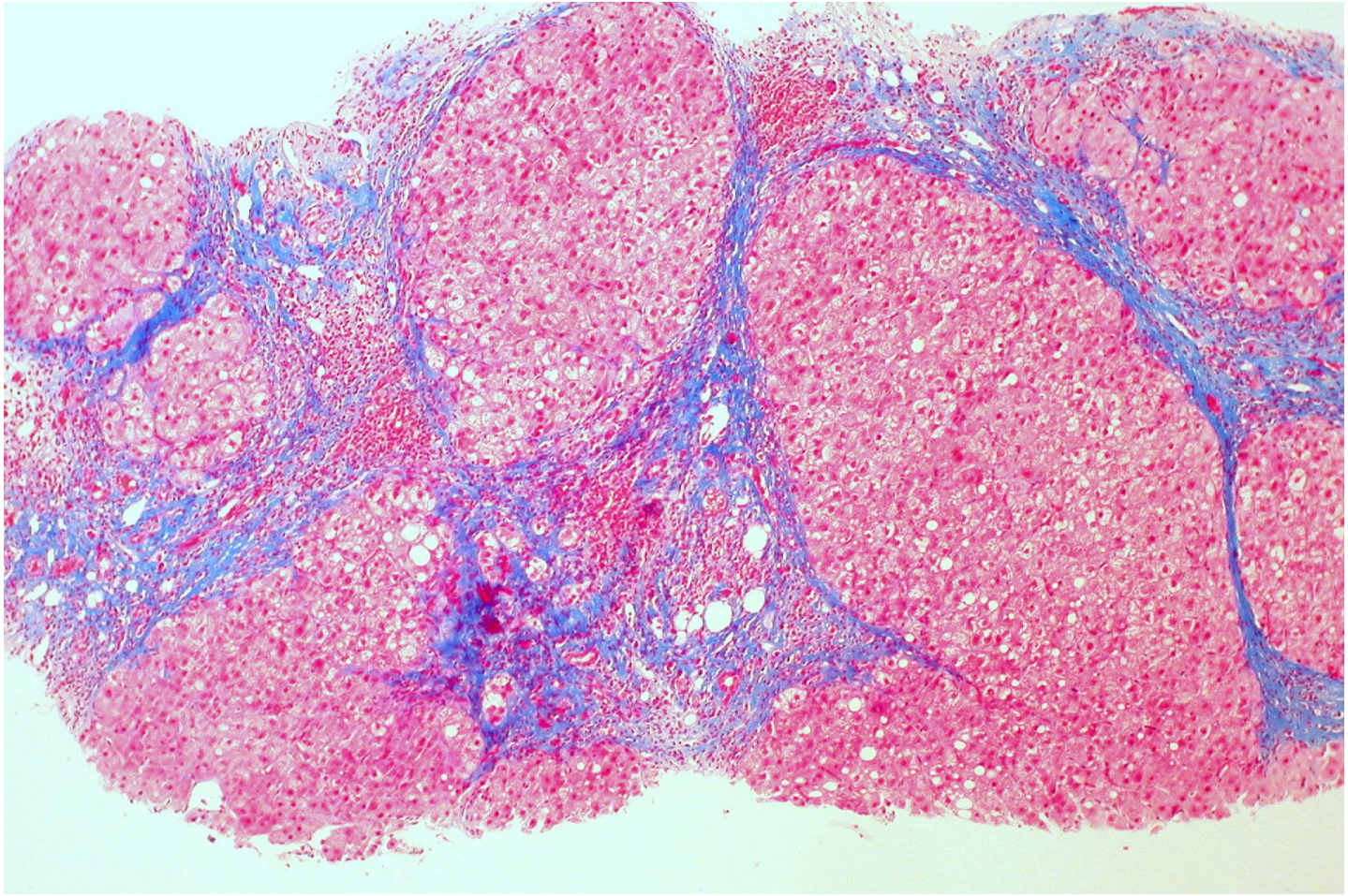
Markers of inflammation and immune cell activation are typically elevated in cirrhotic patients especially in the decompensated disease stage:

- C-reactive protein (CRP)
- Procalcitonin (PCT)

- Liver ultrasound to assess the severity of cirrhosis.
- Liver biopsy to identify liver cell changes & alterations in the lobular structure.
- Prolonged prothrombin time (11-12sec)
- Rarely are diseases of the bile ducts, such as primary sclerosing cholangitis, causes of cirrhosis. Imaging of the bile ducts, such as ERCP or MRCP (MRI of biliary tract and pancreas) may aid in the diagnosis.
- upper endoscopy (to see if esophageal varices are present)
- CT scan of the abdomen



Liver Cirrhosis with ascitis



Trichrome stain, showing cirrhosis as a nodular texture surrounded by fibrosis (wherein collagen is stained blue)

Treatment & Prevention

3

Treatment for cirrhosis varies based on what caused it and how far the disorder has progressed. Some treatments your doctor might prescribe include:

- beta blockers or nitrates (for portal hypertension)
- quitting drinking (if the cirrhosis is caused by alcohol)
- banding procedures (used to control bleeding from esophageal varices)
- intravenous antibiotics (to treat peritonitis that can occur with ascites)
- hemodialysis (to purify the blood of those in kidney failure)
- lactulose and a low protein diet (to treat encephalopathy)
- Liver transplantation is an option of last resort, when other treatments fail.
- All patients must stop drinking alcohol. Medications, even over-the-counter ones, should not be taken without consulting your doctor.

Prevention

- Practicing sex with a barrier method can reduce the risk of getting hepatitis B or C. The U.S. Centers for Disease Control and Prevention Trusted Source recommend that all infants and at-risk adults (such as healthcare providers and rescue personnel) be vaccinated against hepatitis B.
- Limiting alcohol intake or avoiding alcohol, eating a balanced diet, and getting adequate exercise can prevent or slow cirrhosis.
- Vaccination of susceptible patients should be considered for hepatitis A and hepatitis B. Treating the cause of cirrhosis prevents further damage; for example, giving oral antivirals such as entecavir and tenofovir where cirrhosis is due to hepatitis B prevents progression of cirrhosis. Similarly, control of weight and diabetes prevents deterioration in cirrhosis due to non-alcoholic fatty liver disease.

Thank you