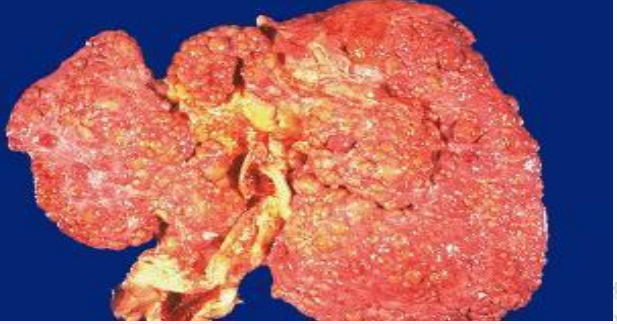

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LIVER CIRRHOSIS AND ITS COMPLICATIONS

MED341

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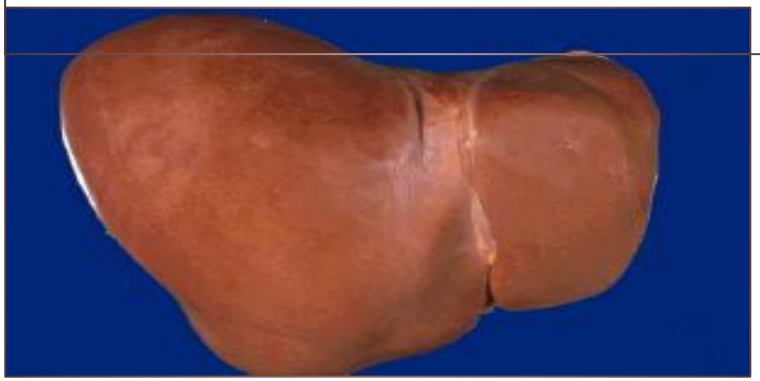
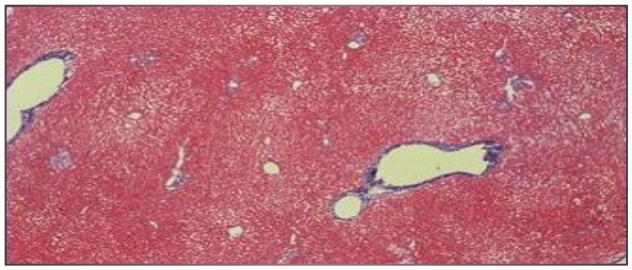
OBJECTIVES

- To know cirrhosis, definition, causes and complications
- To understand pathophysiology of cirrhosis complications
- To known how to approach patient with cirrhosis and its complications

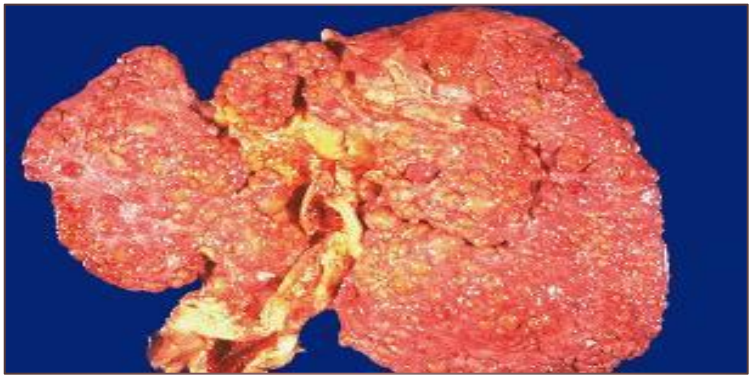
CIRRHOSIS: late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules.

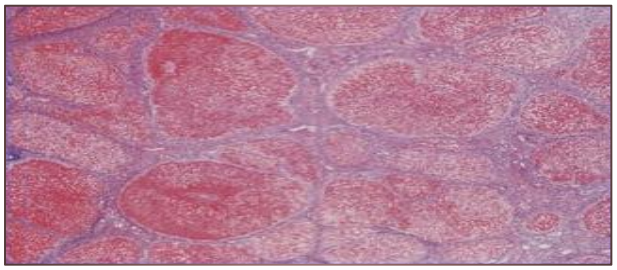
NORMAL LIVER





CIRRHOTIC LIVER





- The final stage of any chronic liver inflammation
- Irreversible in its advanced stages, can be reversed in some if underlying cause is treated.

CAUSES OF CIRRHOSIS

Commonest

- Viral (HBV+- HDV, HCV)
- Non-alcoholic steatohepatitis (NASH)
- Alcoholic steatohepatitis (ASH)

Other causes

- Autoimmune

(AIH, PBC, PSC)

- Metabolic & Hereditary

WD, A1AT, HH

- Vascular

BCS, HF

- Biliary

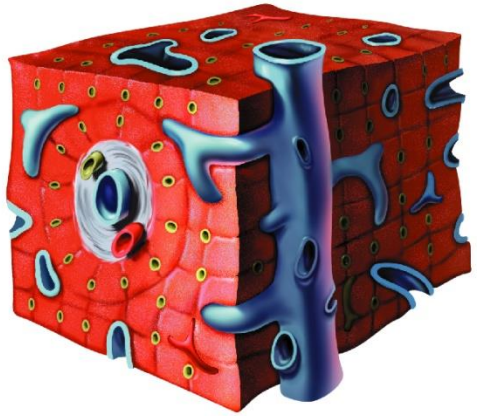
SC

- Drugs
- Others (polycystic disease, granulomatous disease….)

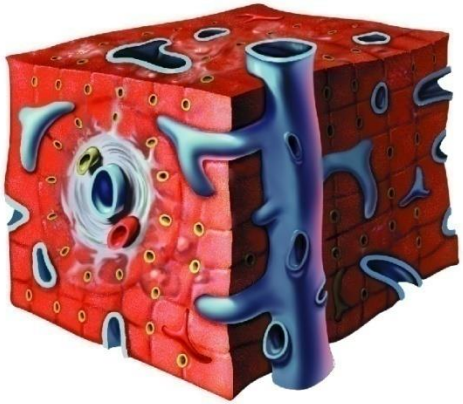
AIH: Autoimmune hepatitis
PBC: Primary biliary cholangitis
PSC: Primary sclerosing cholangitis
WD: Wilson disease
A1AT: alpha-1 antitrypsin deficiency
HH: hereditary hemochromatosis.
BCS: budd-chiari syndrome
HF: Heart failure
SC: sclerosing cholangitis

HISTOLOGIC STAGING

Stage 0



Stage 1



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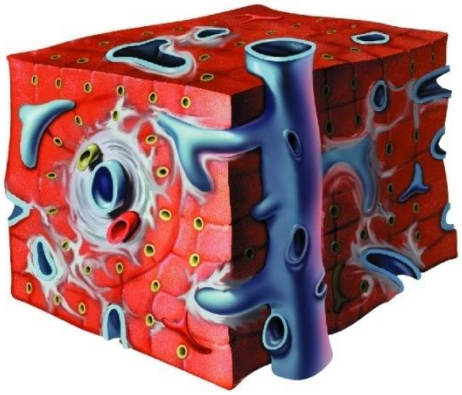
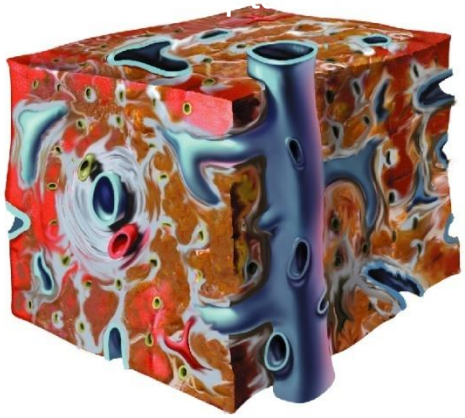
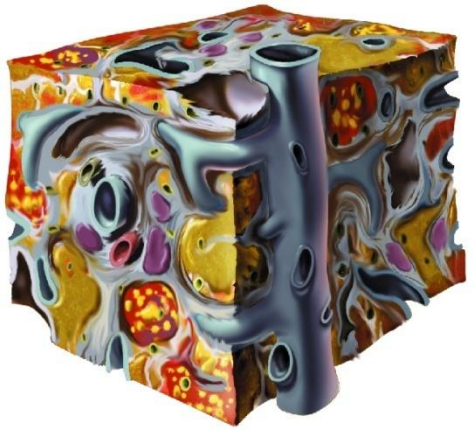


Stage 3



Stage 4



PORTAL HYPERTENSION

-developed as complication of cirrhosis and is the beginning and requirement for most cirrhosis complications

Cirrhosis

1-Structural changes

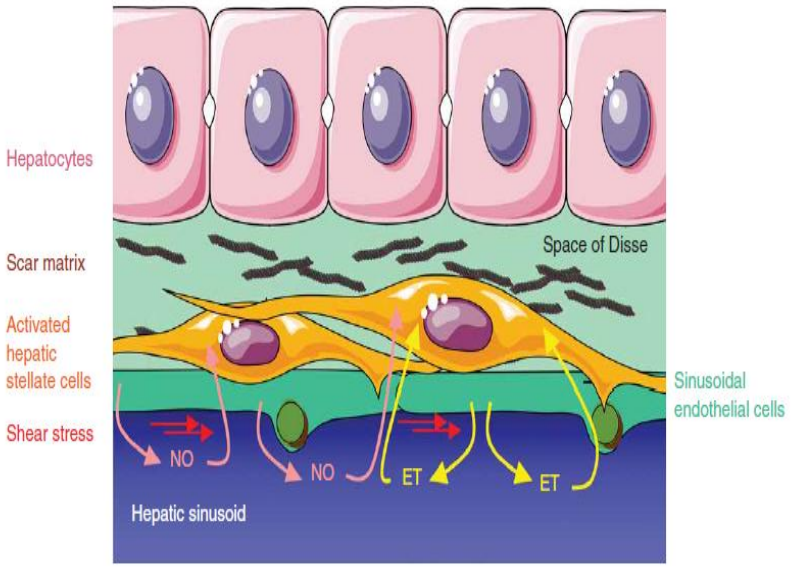
Distortion of the liver microcirculation by:
-fibrosis, nodules, angiogenesis, and vascular occlusion

→ PORTAL HYPERTNSION

2-Dynamic changes

Hepatic stellate cells are activated into myofibroblasts >>
fibrogenesis and contractile potential
(sinusoids, vascular smooth of the hepatic vasculature)

The dynamic changes due to:
-increased production of vasoconstrictors (eg, endothelins, angiotensin-II, norepinephrine, thromboxane A2)
- reduced release of endothelial vasodilators (eg, nitric oxide)



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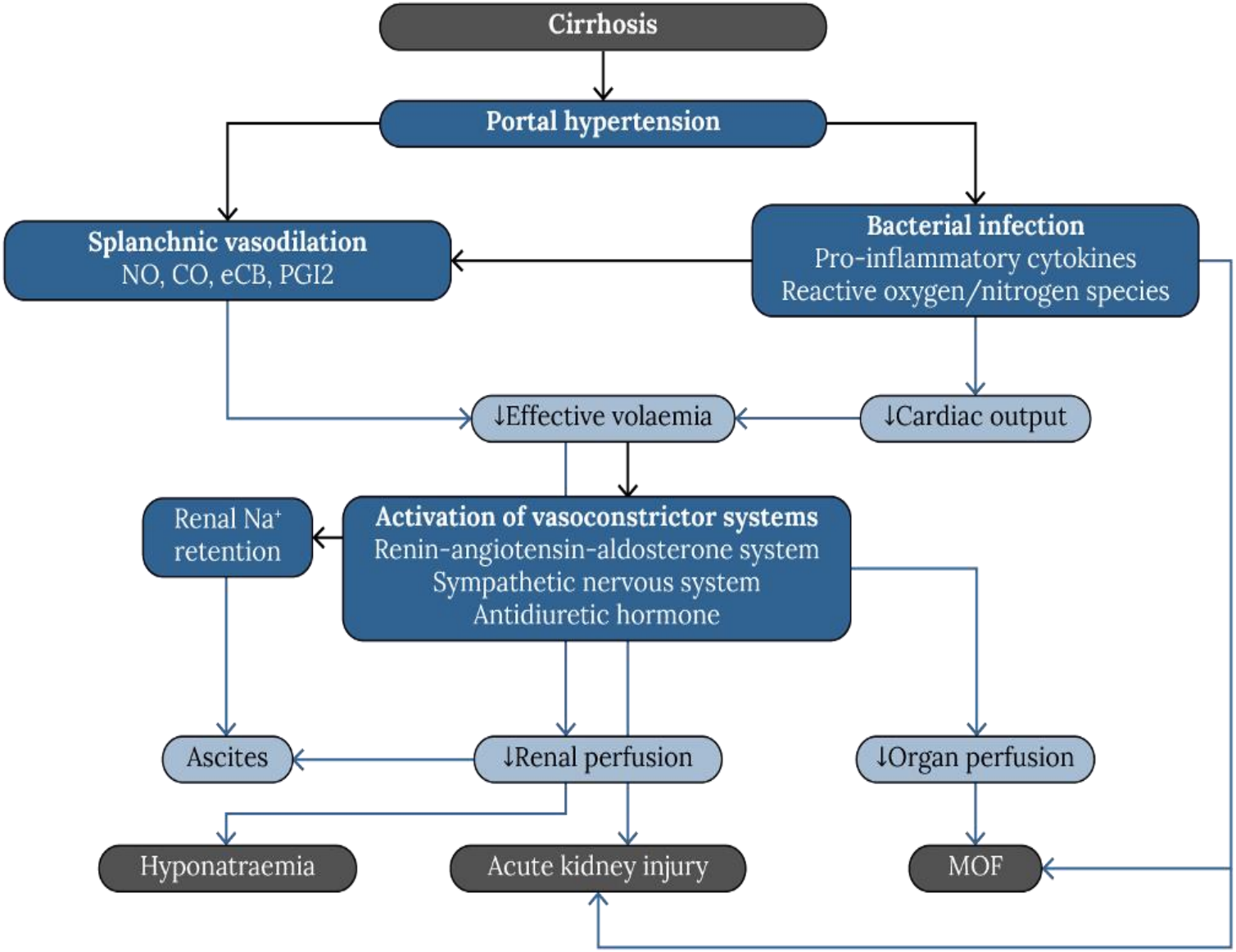
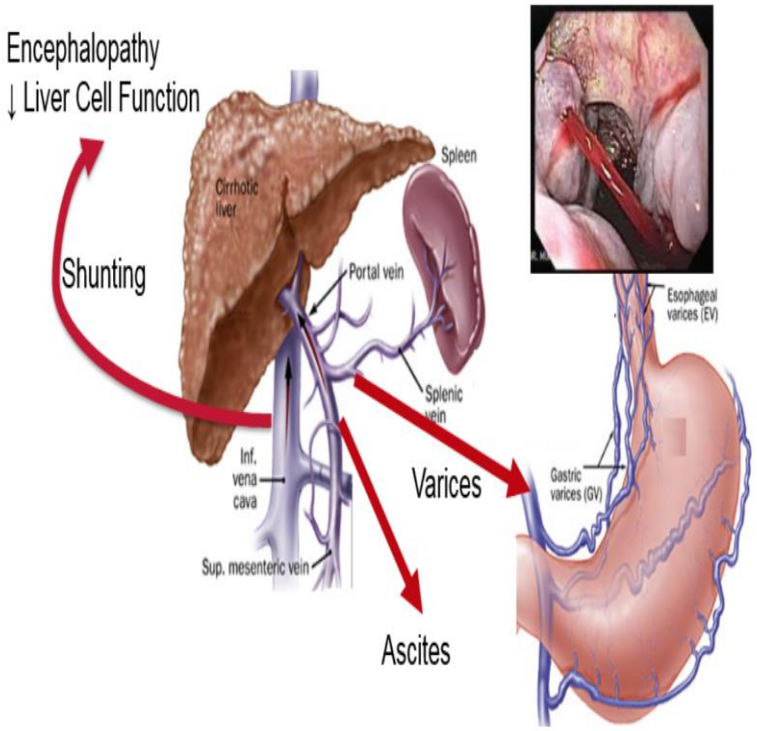
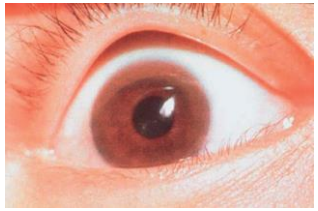

Cirrhosis
Portal hypertension
Splanchnic vasodilation
NO, CO, eCB, PGI2
Bacterial infection
Pro-inflammatory cytokines
Reactive oxygen/nitrogen species
↓Effective volaemia
↓Cardiac output
Renal Na+ retention
Activation of vasoconstrictor systems
Renin-angiotensin-aldosterone system
Sympathetic nervous system
Antidiuretic hormone
Ascites
↓Renal perfusion
↓Organ perfusion
Hyponatraemia
Acute kidney injury
MOF

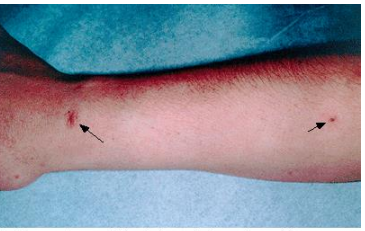
COMMON CIRRHOSIS COMPLICATIONS

- Variceal hemorrhage *(separate lecture)*
- Ascites
  - Asictes +- refractory ascites
  - Spontaneous Bacterial Peritonitis
  - Hepatorenal syndrome
- Hepatic Encephalopathy
- Pulmonary
  - Hepatic hydrothorax (similar to ascites)
  - Hepatopulmonary syndrome
  - Portopulmonary HTN
- Hepatocellular carcinoma



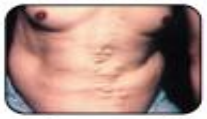
Once a patient develops complications of cirrhosis, they are considered to have ***Decompensated Cirrhosis***



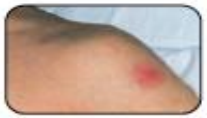


Spider angiomas This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left. Pressure over the central vessel with the end of a paper clip or a glass slide causes the entire lesion to blanch. Similar lesions can be seen in patients with cirrhosis, and are most commonly seen on the upper chest, face, and back.

3 Chest
Loss of body hair

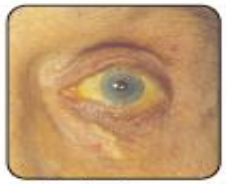


Gynaecomastia



Spider naevi

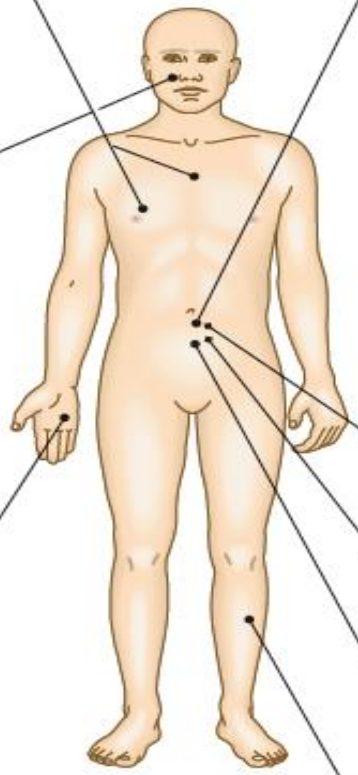
2 Face
Jaundice
Spider naevi
Parotid swelling
Rhinophyma



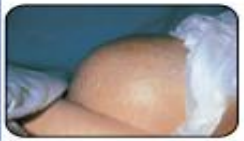
Xanthelasma and jaundiced sclera in a patient with chronic cholestasis

1 Hands
Clubbing
Dupuytren's contracture
Leuconychia
Smooth nails (from scratching)
Bruising
Flapping tremor (when arms outstretched and hands dorsiflexed)

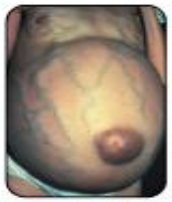
Palmar erythema



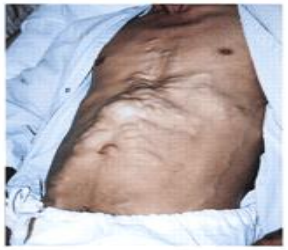
4 Abdomen: inspection
Scars
Distension
Movement
Veins
Testicular atrophy



Abdominal swelling in ascites



Dilated abdominal wall veins (caput medusae)



5 Abdomen: palpation
Hepatomegaly
Splenomegay

6 Abdomen: percussion
Ascites

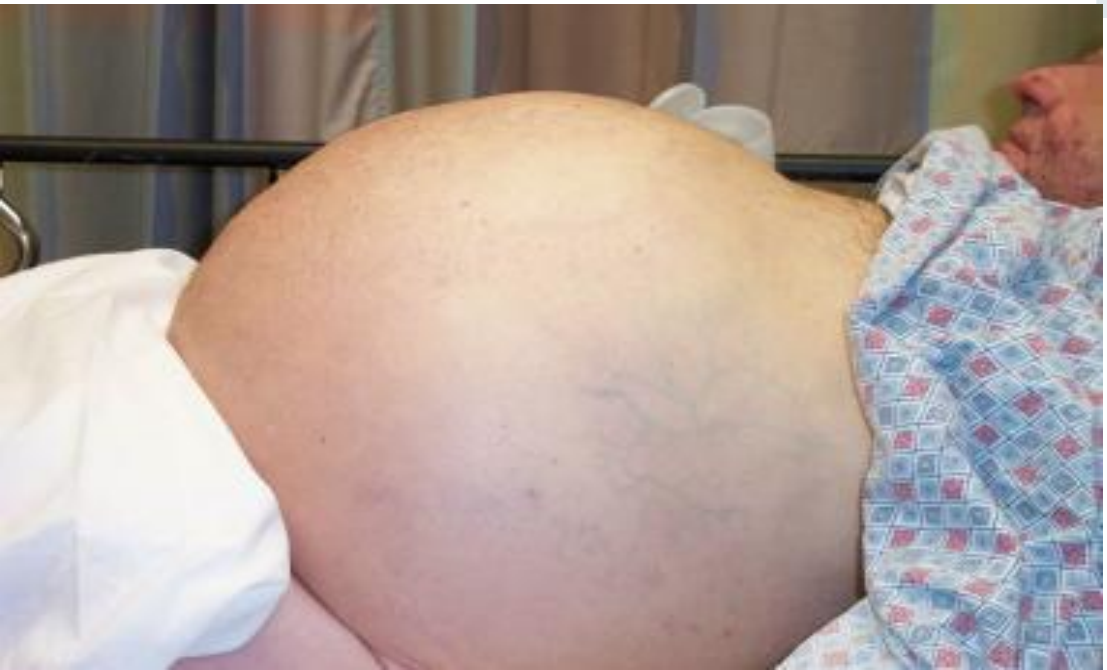
7 Abdomen: auscultation
Bowel sounds
Hepatic bruit

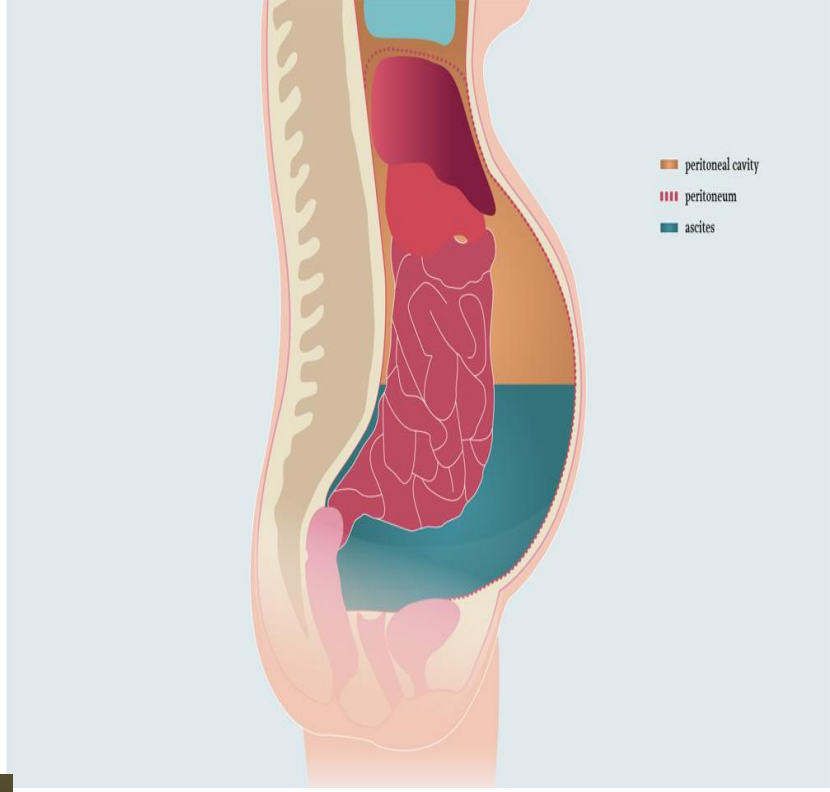
8 Legs
Bruising
Oedema

Observation

- Unkempt
- Smell of alcohol or fetor hepaticus
- Race
- Encephalopathy

ASCITES





ASCITES

- Pathologic accumulation of fluid within the peritoneal cavity
- Most common complication of cirrhosis
- Causes of Ascites:
  1. 85% of due to cirrhosis
  2. 15% other causes
- 1,500 mL of fluid must be present before flank dullness is detected.
- Shifting dullness: 83% sensitivity and 56% specificity in detecting ascites.
- If no flank dullness is present less likely ascites (< 10%).

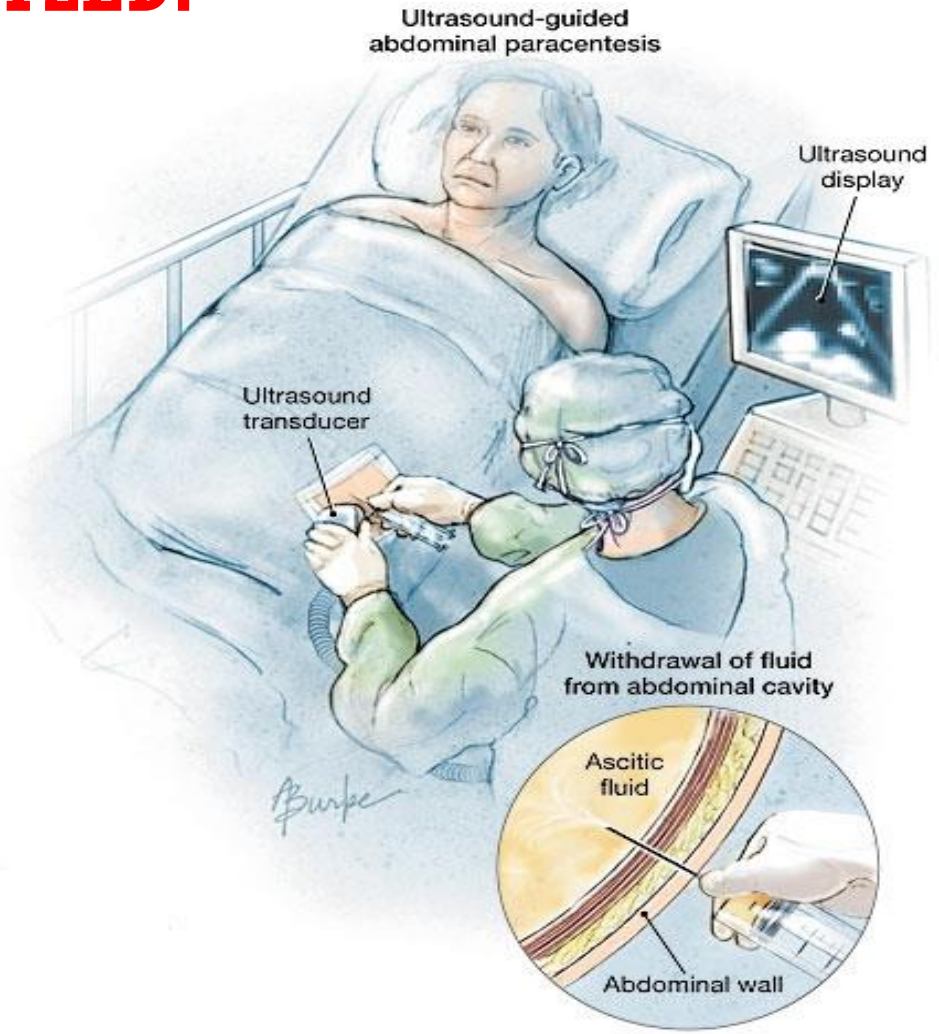
ASCITES

- First step in development of ascites

  >>is the presence of significant portal hypertension

- Poor prognosis (unless Liver Tx)
  - Two-year survival of patients with ascites is approximately 50%

ANY NEW ASCITES SHOULD BE TAPPED AND ANALYZED!



ASCITIC FLUID ANALYSIS

ROUTINE	OPTIONAL (WHEN THERE IS SUSPICION OF INFECTION)	UNUSUAL	UNHELPFUL
Cell count and differential	Culture in blood culture bottles	AFB smear and culture	pH
Albumin	Glucose	Cytology	Lactate
Total protein	Lactate dehydrogenase	Triglyceride	Cholesterol
	Amylase	Bilirubin	Fibronectin
	Gram's stain		Glycosaminoglycans

*Abbreviation: AFB, acid-fast bacteria. *Adapted from Runyon.[17] Reprinted with permission from Saunders Elsevier.*

Measure :

Serum-to-Ascites Albumin Gradient (SAAG)

SERUM-TO-ASCITES ALBUMIN GRADIENT (SAAG)

High SAAG ≥1.1 g/dl (11 g/L)

- Cirrhosis
- Heart failure/constrictive pericarditis
- Alcoholic hepattis
- Budd chiari
- Massive hepatic metastases

Low SAAG <1.1 g/dL 11 g/L)

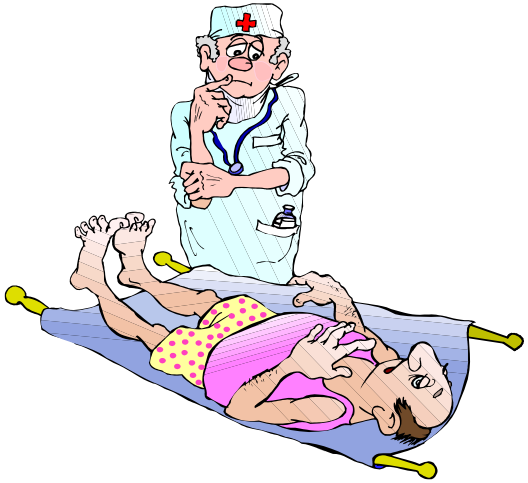
- Peritoneal carcinomatosis
- Peritoneal tuberculosis
- Secondary peritonitis
- Pancreatitis
- Serositis
- Nephrotic syndrome

INITIAL TREATMENT OF ASCITES

- **1-Dietary sodium restriction**
  - Limiting sodium intake to 88 meq (2000 mg) per day
- **2-Diuretics** (most successful therapeutic regimen is the *combination* of Spironolactone and Furosemide)
  - Monitor electrolytes and kidney function

- Discontinue non-steroidal anti-inflammatory drugs
- Rx of underlying cause
- Evaluation for liver transplantation

REFRACTORY ASCITES



- ~10%

Defined as ascites that:

- Unresponsive to sodium-restricted diet and high dose diuretic treatment

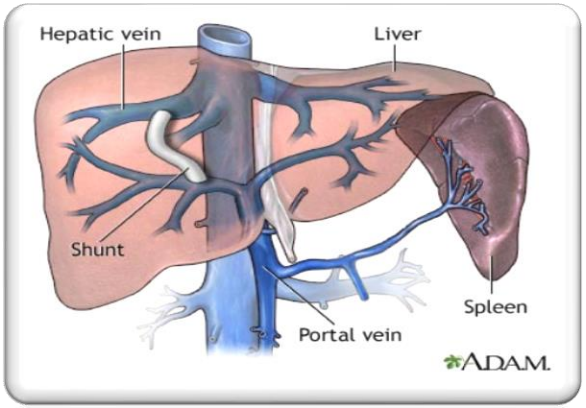
Or

- Development of clinically significant complications of diuretics

MANAGEMENT LINES

- Serial therapeutic paracenteses (LVP)

  +albumen (if draining> 5 L of fluid).
- Liver transplantation
- Trans-jugular intrahepatic portosystemic stent-shunt (TIPS)
- Peritoneo-venous shunt



SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Development of a bacterial infection in the peritoneum, despite the absence of an obvious source for the infection.

- The diagnosis is established by
  - PMN count (>250 cells/mm3)
  - A positive ascitic fluid bacterial culture
- Organisms

  -Most cases of SBP are due to gut bacteria such as *E. coli* and *Klebsiella*

  -sometimes others: streptococcal, staphylococcal , Enterococcus infections.

Clinical manifestations:
(all, some, sometimes-none)

- Fever
- Abdominal pain/tenderness
- Altered mental status

SBP

Rx

1. **Antibiotics:** Cefotaxime or a similar ***third-generation cephalosporin*** -treatment of choice for suspected SBP; it used to cover 95% of the flora including the common organisms

2. **Albumin:** to high risk patient

(the creatinine is >1 mg/dL (88 micromol/L), the blood urea nitrogen is >30 mg/dL (10.7 mmol/L), or the total bilirubin is >4 mg/dL (68 micromol/L)

- Why: help in decreasing renal failure
- Occur in 30-40% of SBP (major cause of death)

HEPATORENAL SYNDROME (HRS)

Acute renal failure (Functional)

Require presence of cirrhosis and ascites

- Dx by exclusion (NB: most common cause of acute renal failure in cirrhosis is pre-renal not HRS)
- 2 types
  - Type I: rapid, aggressive
  - Type II : slow, less aggressive
- Rx
  - Correct underlying cause
  - Albumin
  - Vasoconstrictors (Terlipression, octeriotide, midodrine, epinephrine)
  - Hemodialysis
  - Liver transplantation.

HEPATIC HYDROTHORAX

- Pleural effusion in a patient with cirrhosis and no evidence of underlying cardiopulmonary disease.
- Commonly Rt side
- 5-10% of cirrhosis patients.
- Cause: movement of ascitic fluid into the pleural space through defects in the diaphragm.

- Dx
  - reveals a transudative fluid
  - serum to fluid albumin gradient greater than 1.1

- Management similar to ascites

HEPATOPULMONARY SYNDROME (HPS)

Triad:

- Liver disease (liver disease, portal hypertension, or portosystemic shunts)
- Increased alveolar-arterial gradient while breathing room air
- Evidence for intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations (shunting)

-Mild hypoxemia is common w/o HPS (ascites)

PORTOPULMONARY HTN

- Refers to the presence of pulmonary hypertension in the coexistent portal hypertension

- Prevalence in cirrhotic patients is approximately 2%

- Diagnosis:
  - Suggested by echocardiography
  - Confirmed by right heart catheterization

HEPATIC ENCEPHALOPATHY (HE)

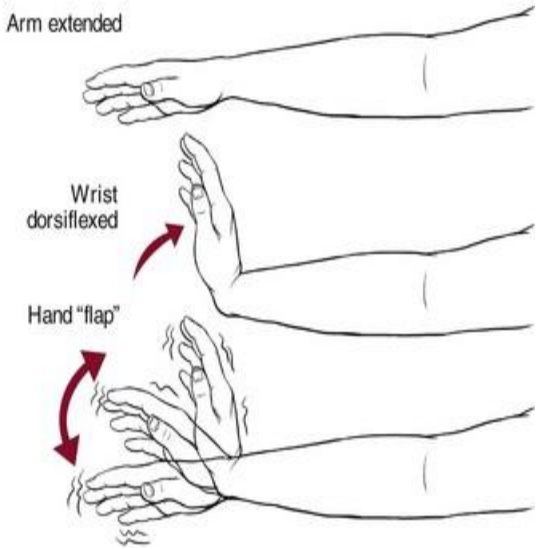
DEFINITION OF HE

- Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunt.

- It manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

Grading system for hepatic encephalopathy

Grade	Mental status	Asterixis	EEG
I	Euphoria/depression	Yes/no	Usually normal
	Mild confusion		
	Slurred speech		
	Disordered sleep		
II	Lethargy	Yes	Abnormal
	Moderate confusion		
III	Marked confusion	Yes	Abnormal
	Incoherent		
	Sleeping but arousable		
IV	Coma	No	Abnormal



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PATHOPHYSIOLOGY OF HE

Different mechanisms

- Neurotoxin (ammonia)
- Blood-to-brain transport of neurotransmitter

- →activation of inhibitory neurotransmitter systems (gamma-aminobutyric acid, serotonin)
- → impairment of excitatory neurotransmitter systems (glutamate, catecholamines)

>>>> <u>enhanced neural inhibition</u>

Sepsis, neuroinflammation, and alterations in gut flora appear to be additional factors.

PRECIPITANTS OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

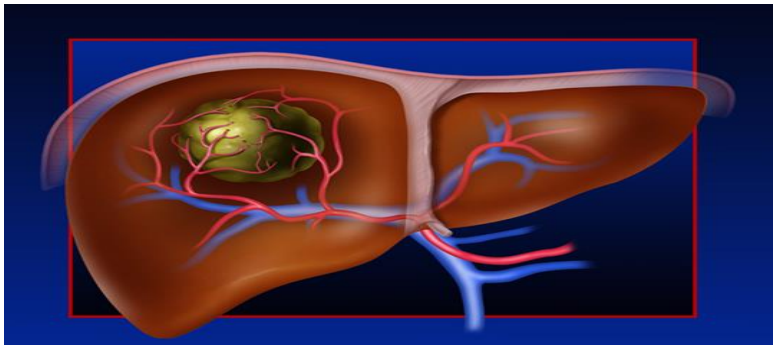
- **Drugs**
  - Benzodiazepines
  - Narcotics
  - Alcohol
- **Increased ammonia production, absorption or entry into the brain**
  - Excess dietary intake of protein
  - Gastrointestinal bleeding
  - Infection
  - Electrolyte disturbances such as hypokalemia
  - Constipation
  - Metabolic alkalosis
- **Dehydration**
  - Vomiting
  - Diarrhea
  - Hemorrhage
  - Diuretics
  - Large volume paracentesis
- **Portosystemic shunting**
  - Radiographic or surgically placed shunts
  - Spontaneous shunts
- **Vascular occlusion**
  - Hepatic vein thrombosis
  - Portal vein thrombosis
- **HCC**

RX

1. Identify and treat precipitating factors for HE

2. Measures to lower the blood ammonia concentration
   - Lactulose is the first choice for treatment

   - Other medications:
     - Rifaximin (nonabsorbable oral antibiotic)
     - LOLA(L-ornithine-L-aspartate, which stimulates the metabolism of ammonia)
     - Oral BCAAs (branched-chain amino acids (BCAA)



HEPATOCELLULAR CARCINOMA (HCC)

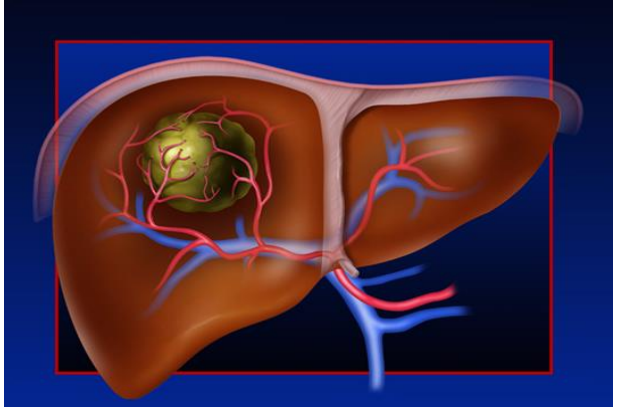
- Patients with cirrhosis have a markedly increased risk of developing hepatocellular carcinoma

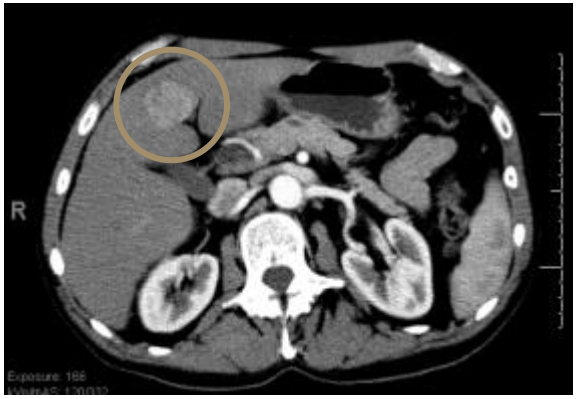
- Incidence in compensated cirrhosis is ~3%/year
- 25-30% in 10 y.

TESTS TO DIAGNOSE HCC

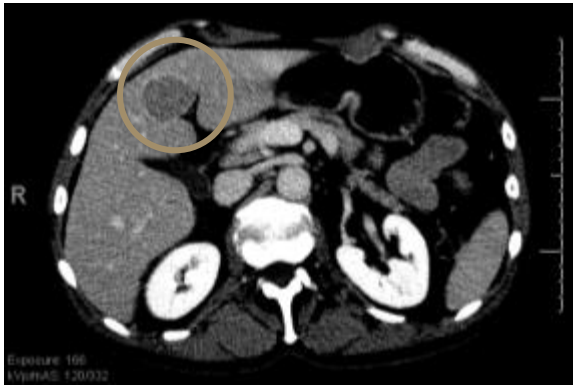
- Radiology (most important)
- Biopsy
- Blood tests: alphafetoprotein (AFP) high in some patients

HCC DIAGNOSIS: DYNAMIC IMAGING





During early arterial phase on CT, an HCC appears brighter than surrounding liver



In later portal venous phase, the HCC appears darker than surrounding liver (washout)

- HCCs are hypervascular
- Tumor blood supply:
  - 100% hepatic artery
- Liver parenchymal blood supply:
  - 30% hepatic artery
  - 70% portal vein
- Dynamic imaging (MRI, CT) follows tumor density with time after IV contrast bolus
  - Requires both arterial enhancement and washout

HCC RX OPTIONS

Options (depends of the stage)

- Surgical (resection, liver transplantation)
- Ablation (radiofrequency (RFA), or alcohol injection
- Embolization (TACE; trans-arterial chemoembolization or TARE: trans-arterial radio-embolization)
- Chemotherapy
- Palliative

LIVER TRANSPLANTATION

- Liver transplantation is the definitive treatment for patients with decompensated cirrhosis

- Depends upon the severity of disease, quality of life and the absence of contraindications

OTHER RECOMMENDATIONS

- **Screening in cirrhosis:**
  - HCC surveillance with ultrasound Q6 months
  - Endoscopy for varices

Avoidance of additional insults

- Avoidance of:
  - Alcohol
  - Herbal medications (of unknown liver safety)
  - Careful use of potentially hepatotoxic medicine if needed, and no alternatives.

Vaccinations

All cirrhotic should be vaccinated to:

- Hepatitis A and B
- Pneumococcal
- Influenza

HOW TO APPROACH PATIENT WITH CIRRHOSIS?

- Symptoms
- Signs
- Lab
- Management

CLINICAL MANIFESTATIONS

- No symptoms (Most patients in early cirrhosis)

- Symptoms of cirrhosis (sometimes non-specific symptoms)

- Symptoms of decompensations (when liver start to fail.)

HISTORY

Presenting symptoms	Past and drug History	Family history	Social history
1-Asymptomatic 2-Nonspecific constitutional symptoms, such as fatigue, weakness, and weight loss, etc.) 3-Symptoms of decompensation -abdominal distension due to ascites and hepatomegaly, -coffee-ground vomitus and black stool (melena) secondary to GI hemorrhage -altered mental status in hepatic encephalopathy -lower extremity swelling -jaundice, and pruritus. Other less common symptoms: respiratory (pulmonary hypertension, hepatic hydrothorax..)	History of liver disease (all chronic liver disease can lead to cirrhosis) Surgery and dental Metabolic syndrome Drugs (MTX, amiodarone, amoxicillin/clavulanateetc..)	Wilson Hemochromaosis Apha-antitrypein Viral hepatitis	Risk-taking behaviors: IV drug use, sexual contact, and tattoos. Alcohol (amount type duration) Travel

CLINICAL FEATURES

Hand and nail features:	Facial features	Chest wall features	Abdominal features
Clubbing Leukonychia Palmar erythema Bruising Cholesterol deposits Dupuytren contracture Cyanosis (in patients with hepatopulmonary syndrome).	Muscle wasting Telangiectasia Bruising Parotid gland swelling Jaundiced sclerae Xanthelasma	Gynecomastia in men Telangectasia	Collateral Bruising Hepatomegaly Splenomegaly Abdominal distension Hepatic bruit Loss of secondary Sexual hair Testicular atrophy in men.

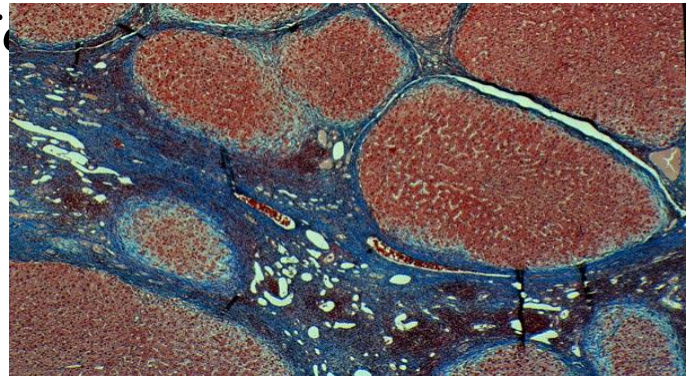
INVESTIGATIONS IN CIRRHOSIS

Lab Test	Radiology
Moderately elevated aminotransferases (often with an AST:ALT ratio >1)	Surface nodularity
Elevated ALP (2 to 3 times the ULN)	Hypertrophy of the caudate or left lobes
Thrombocytopenia	Portosystemic collaterals*
Leukopenia/neutropenia	Ascites*
Anemia	Hepatocellular carcinoma*
Low serum albumin*	Portal/splenic/superior mesenteric vein thrombosis*
Prolonged prothrombin time/elevated INR*	
Hyperbilirubinemia*	
Hyponatremia*	
Elevated serum creatinine*	

* With advanced disease

DIAGNOSIS CONFIRMATION?

To confirm and support the clinical and radi
needed



1-Biopsy (histology)

2-Noninvasive tests

- Serum score systems
- Elastography (e.g fiobroscan)

HOW TO ASSES SEVERITY & PROGNOSIS?

- **Child–Turcotte–Pugh score** or **Child Criteria (CPT score)…see table**

- **MELD score**

(model for end-stage liver disease)

  - MELD = 3.8[serum bilirubin (mg/dL)] + 11.2[INR] + 9.6[serum creatinine (mg/dL)] + 6.4

- others

CPT SCORE FOR CLASSIFICATION OF CIRRHOSIS SEVERITY

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
PT (Seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Score	Class	1-2 Year survival
5-6	A	100-85%
7-9	B	80-60%
10-15	C	45-35%

THANK YOU

Best of Luck