



LIVER CIRRHOSIS AND ITS COMPLICATIONS

MED341

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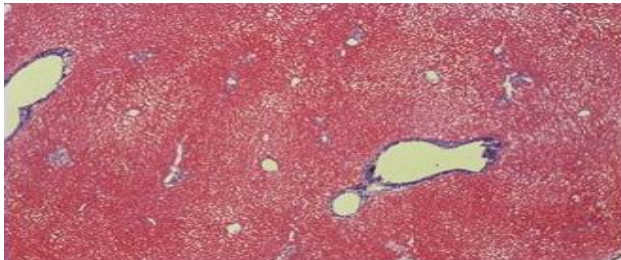
OBJECTIVES

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

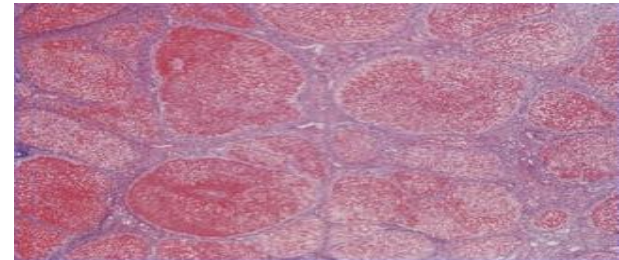
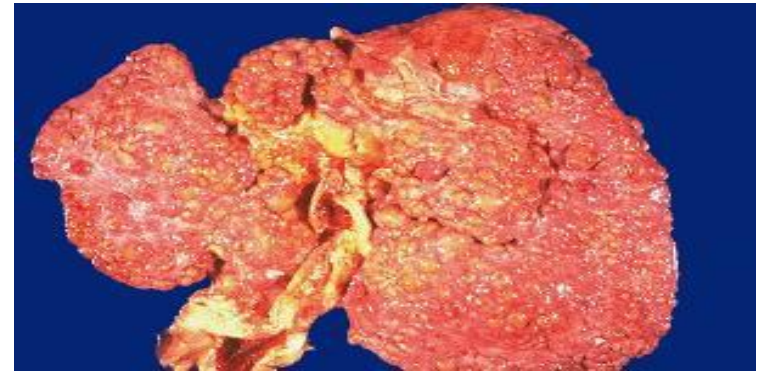


CIRRHOSIS : LATE STAGE OF CHRONIC LIVER INFLAMMATION AND FIBROSIS, IN WHICH LIVER PARENCHYMA IS DISTORTED AND REPLACED BY FIBROUS TISSUE AND REGENERATING NODULES.

NORMAL LIVER



CIRRHOTIC LIVER



- The final stage of any chronic liver inflammation
- Irreversible in its advanced stages



CAUSES OF CIRRHOSIS

Commonest

- Viral (HBV+- HDV, HCV)
- NASH
- ASH

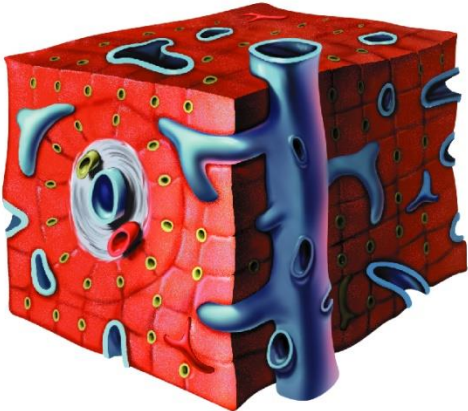
Other causes

- Autoimmune
(AIH, PBC, PSC)
- Metabolic & Hereditary
WD, A1AT, HH
- Vascular
BCS, HF
- Biliary
SC
- Drugs
- Others (polycystic disease,
granulomatous disease....)

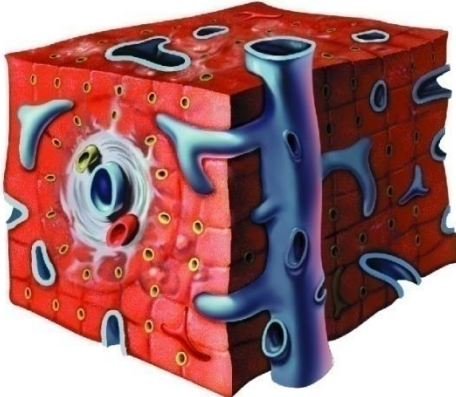


HISTOLOGIC STAGING

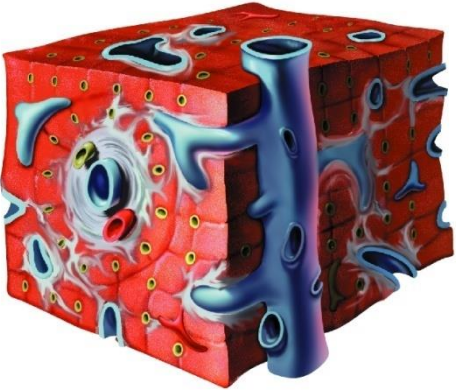
Stage 0



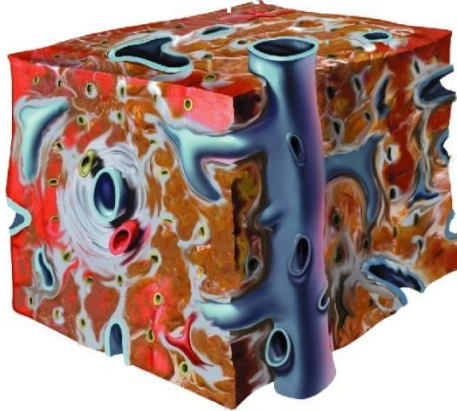
Stage 1



Stage 2



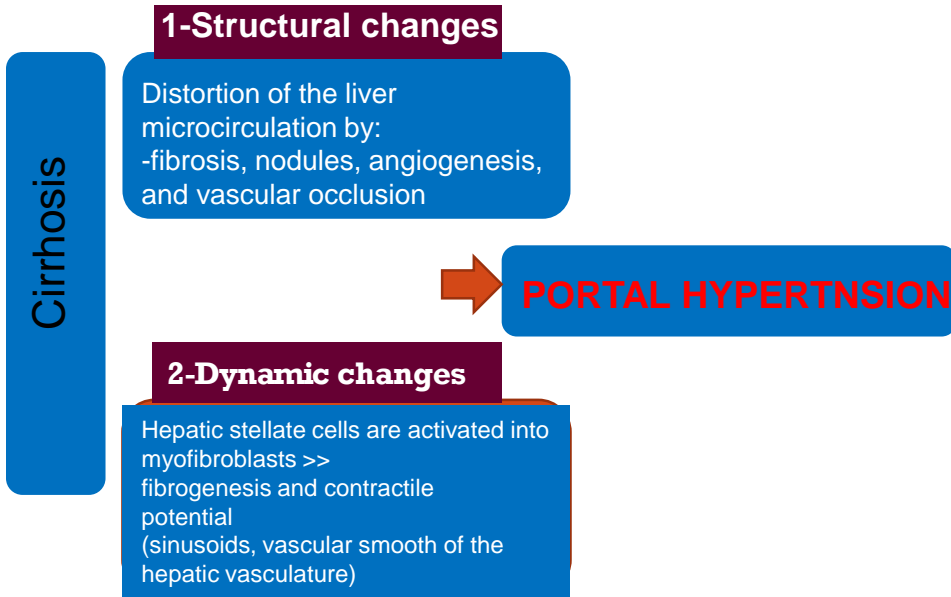
Stage 3



Stage 4

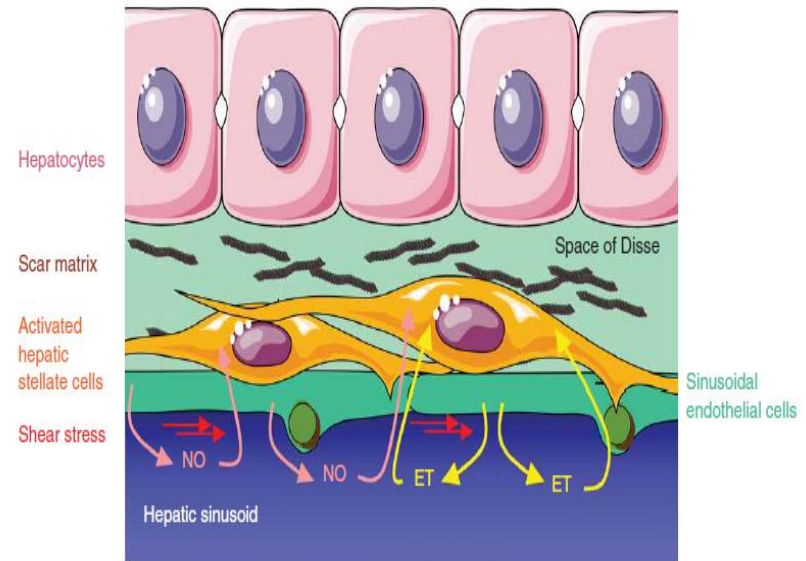


PORTAL HYPERTENSION IS THE BEGINNING AND REQUIREMENT FOR MOST CIRRHOSIS COMPLICATIONS



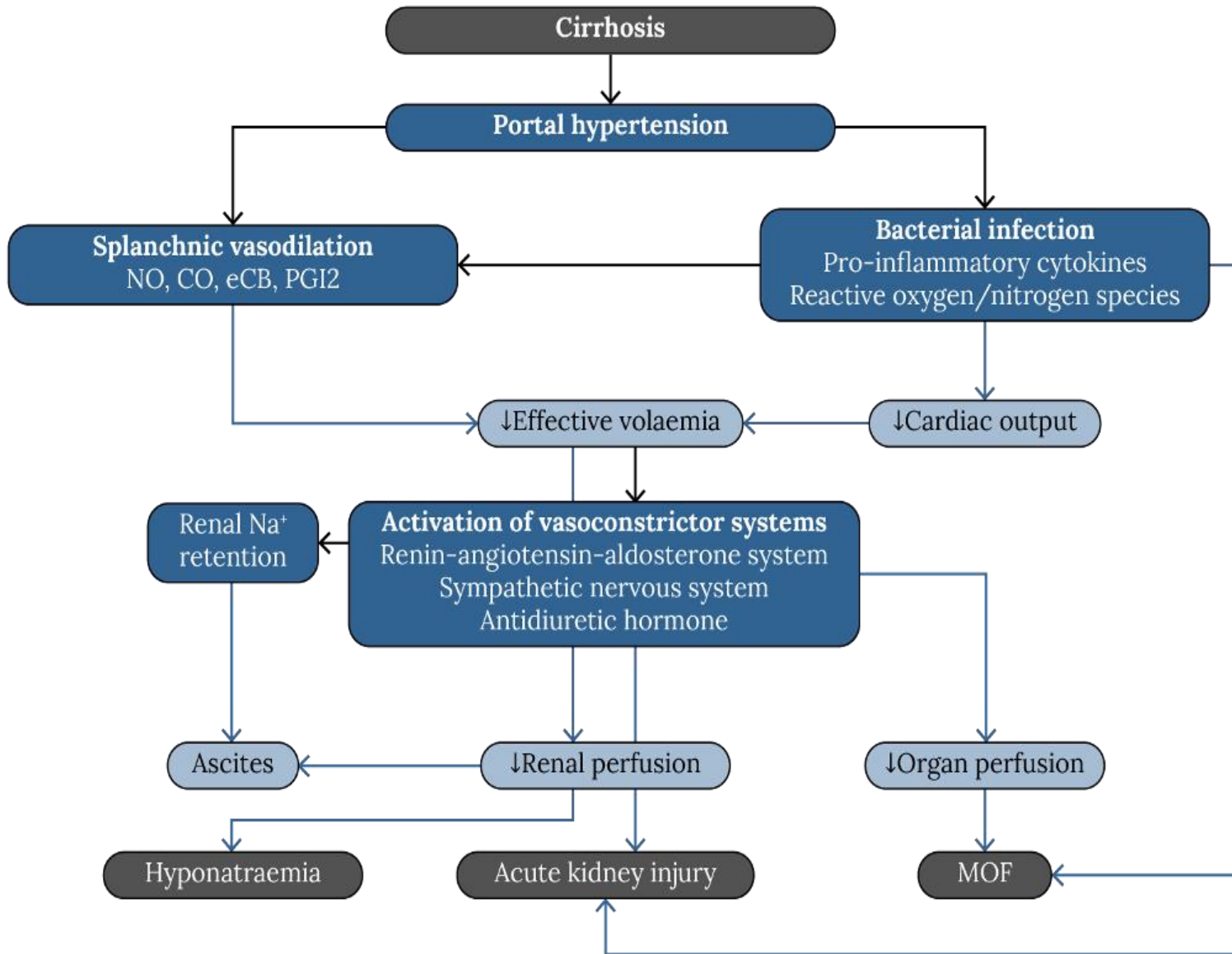
The dynamic changes due to:

- increased production of vasoconstrictors (eg, endothelins, angiotensin-II, norepinephrine, thromboxane A2)
- reduced release of endothelial vasodilators (eg, nitric oxide)



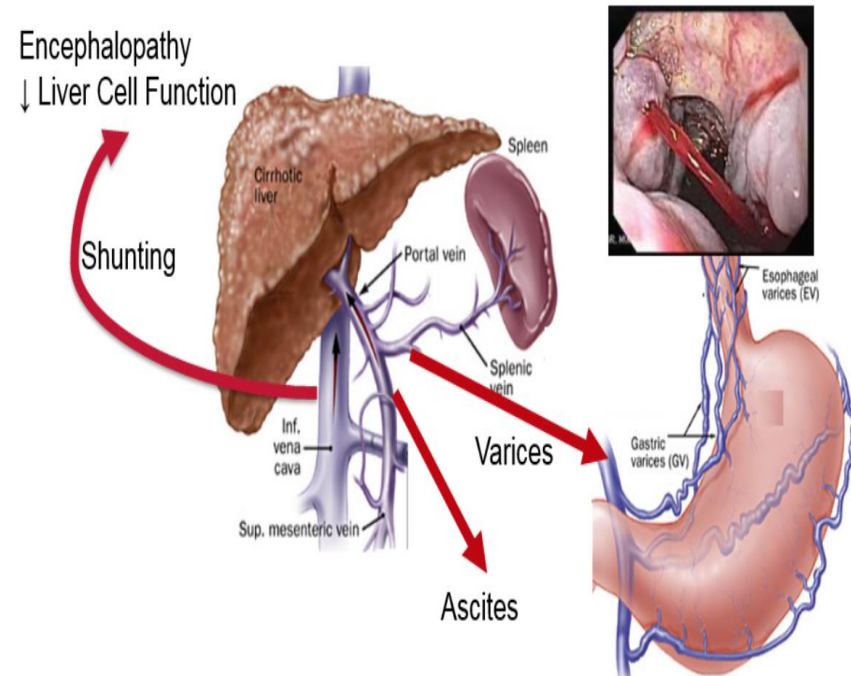
Møller S et al .Scand J Gastroenterol. 2015





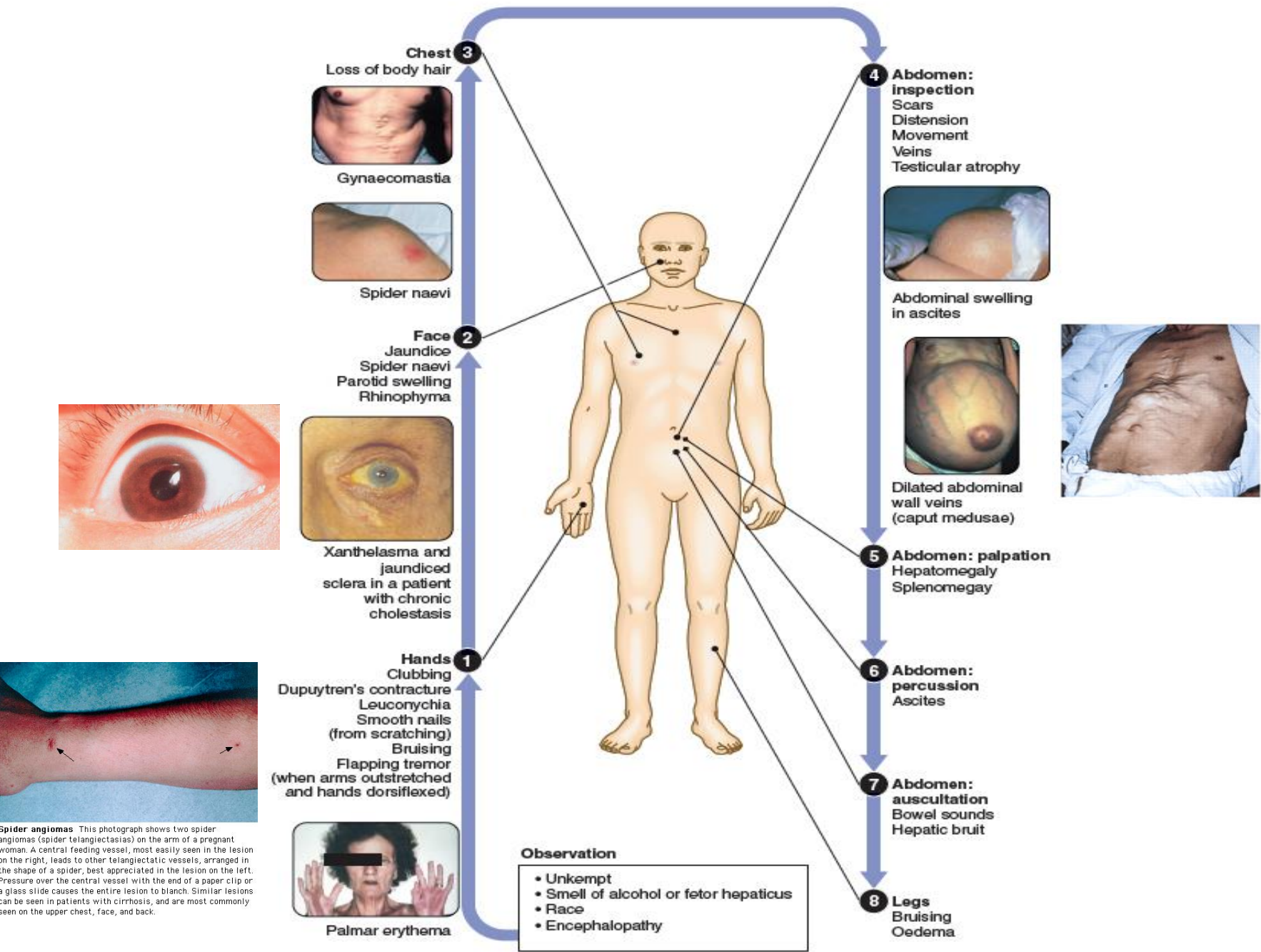
COMMON CIRRHOSIS COMPLICATIONS

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

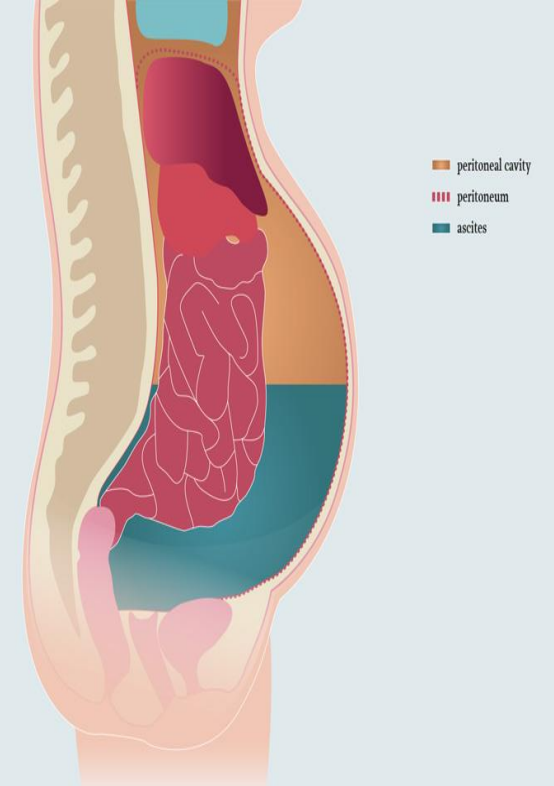


Once a patient develops complications of cirrhosis, they are considered to have **Decompensated Cirrhosis**





ASCITES



ASCITES

- Pathologic accumulation of fluid within the peritoneal cavity
- 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:
 1. 85% of due to cirrhosis
 2. 15% other causes

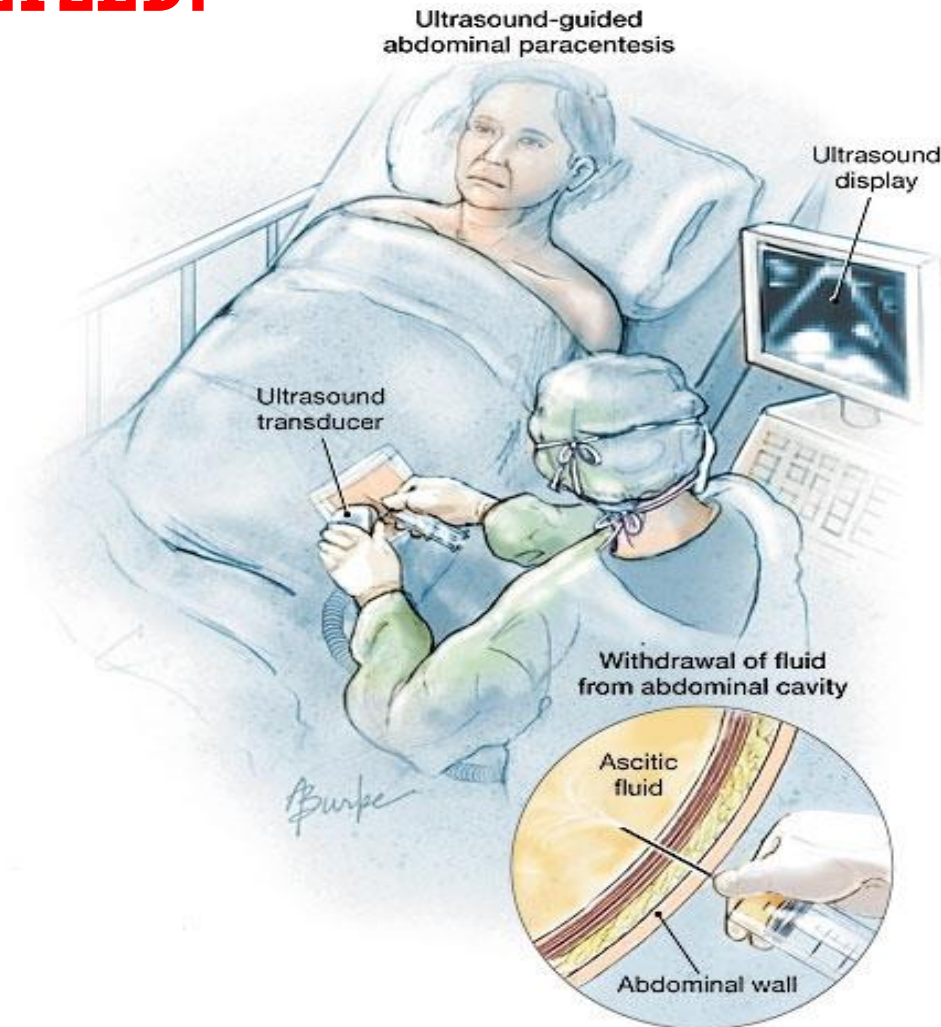


ASCITES

- **Most common complication of cirrhosis**
- **First step in development of ascites is the presence of significant portal HPN**
- **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.* Reprinted with permission from Saunders Elsevier.



Measure **SAAG**



SERUM-TO-ASCITES ALBUMIN GRADIENT (SAAG)

High SAAG ≥ 1.1 g/dL

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

Low SAAG < 1.1 g/dL

- 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

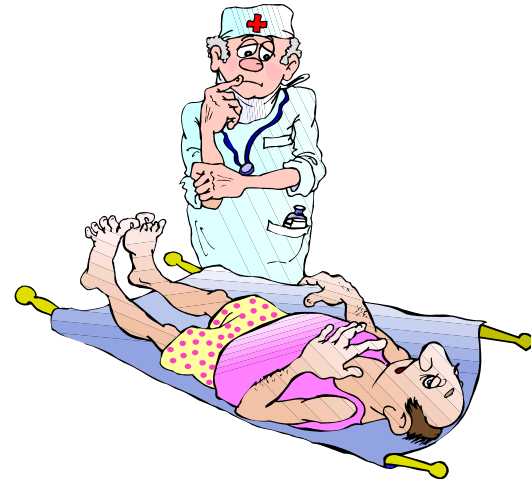


REFRACTORY ASCITES

- ~10%

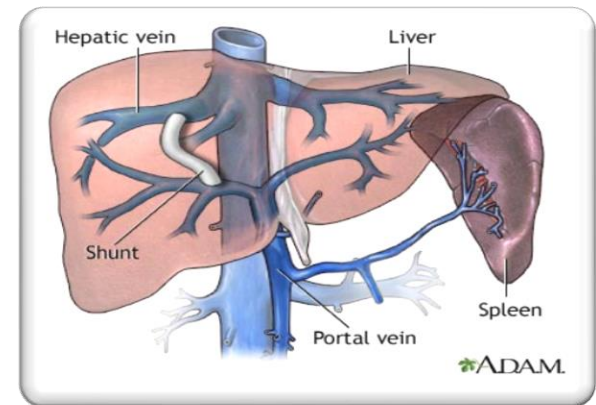
Ascites that:

- Unresponsive to sodium-restricted diet and high dose diuretic treatment
- Development of clinically significant complications of diuretics



MANAGEMENT LINES

- Serial therapeutic paracenteses (LVP)
 - +albumen (if draining > 5 L of fluid).
- Liver transplantation
- Transjugular intrahepatic portosystemic stent-shunt (TIPS)
- Peritoneovenous shunt



SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- Infection of ascitic fluid
- 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 and staphylococcal infections
- Clinical manifestations: (all, some, sometimes-none)
 - Fever
 - Abdominal pain
 - Abdominal 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** must be given 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

Acute renal failure (Functional) – usually Cirrhosis with ascites

- Dx by exclusion (NB: minority of azotemia is not due HRS)
- 2 types
 - Type I: rapid, aggressive
 - Type II : slow, less aggressive
- Rx
 - Correct underlying cause
 - Albumin
 - Vasoconstrictors (Terlipression, octeriotide, midodrine, epinephrine)
 - HD
 - Liver Tx



HEPATIC HYDROTHORAX

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



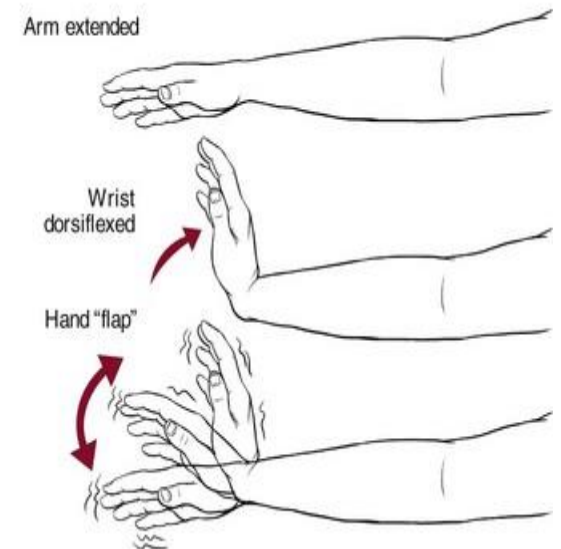
DEFINITION OF HE

- **Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS**
- **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



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)

>>>> enhanced neural inhibition



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

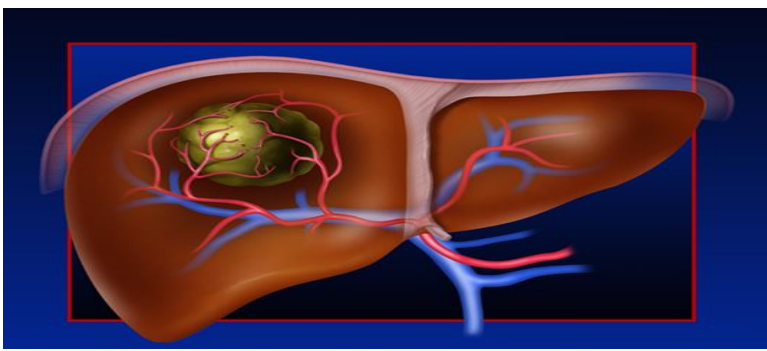
▪ **HCC**



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.

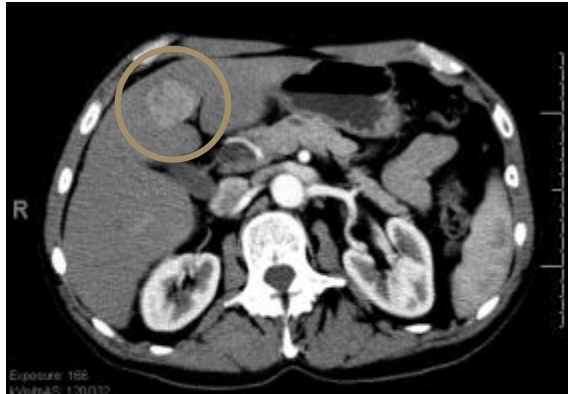
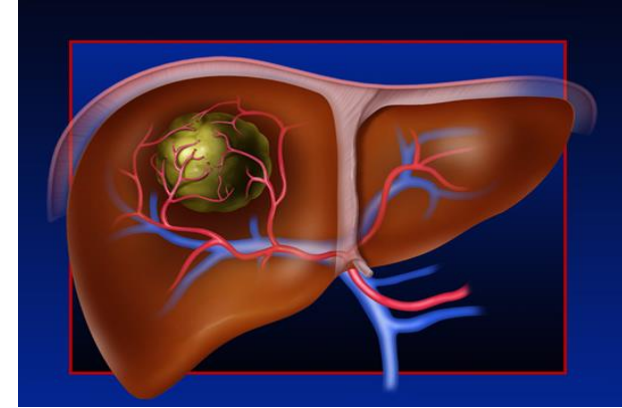


TESTS TO DIAGNOSE HCC

- Blood tests (AFP)
- Radiology (**most important**)
- Biopsy



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:**

- Radiology for HCC surveillance Q6 months for all cirrhosis patients
- Endoscopy for varices

Avoidance of additional insults

- Avoidance of:
 - Alcohol
 - Herbal medications
 - Careful use of potentially hepatotoxic medicine

Vaccinations

All cirrhotic should be vaccinated to:

- Hepatitis A and B
- Pneumococcal vaccine
- Influenza vaccination



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



HISTORY

Presenting symptoms	Past and drug History	Family history	Social history
<p>1-Asymptomatic 2-Nonspecific constitutional symptoms, such as fatigue, weakness, and weight loss, etc.)</p> <p>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.</p> <p>Other less common symptoms: respiratory (pulmonary hypertension, hepatic hydrothorax..)</p>	<p>History of liver disease (all chronic liver disease can lead to cirrhosis)</p> <p>Surgery and dental</p> <p>Metabolic syndrome</p> <p>Drugs (MTX, amiodarone, amoxicillin/clavulanate etc..)</p>	<p>Wilson</p> <p>Hemochromatosis</p> <p>Alpha-1 antitrypsin</p> <p>Viral hepatitis</p>	<p>Risk-taking behaviors: IV drug use, sexual contact, and tattoos.</p> <p>Alcohol (amount type duration)</p> <p>Travel</p>

CLINICAL FEATURES

Hand and nail features:	Facial features	Chest wall features	Abdominal features
Clubbing	Muscle wasting	Gynecomastia in men	Collateral
Leukonychia	Telangiectasia	Telangectasia	Bruising
Palmar erythema	Bruising		Hepatomegaly
Bruising	Parotid gland swelling		Splenomegaly
Cholesterol deposits	Jaundiced sclerae		Abdominal distension
Dupuytren contracture	Xanthelasma		Hepatic bruit
Cyanosis (in patients with hepatopulmonary syndrome).			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)	Increased echogenicity (ultrasound)
Thrombocytopenia	Atrophy of the right lobe
Leukopenia/neutropenia	Hypertrophy of the caudate or left lobes
Anemia	Small, nodular liver*
Low serum albumin*	Ascites*
Prolonged prothrombin time/elevated INR*	Hepatocellular carcinoma*
Hyperbilirubinemia*	Portal/splenic/superior mesenteric vein thrombosis*
Hyponatremia*	Portosystemic collaterals*
Elevated serum creatinine*	

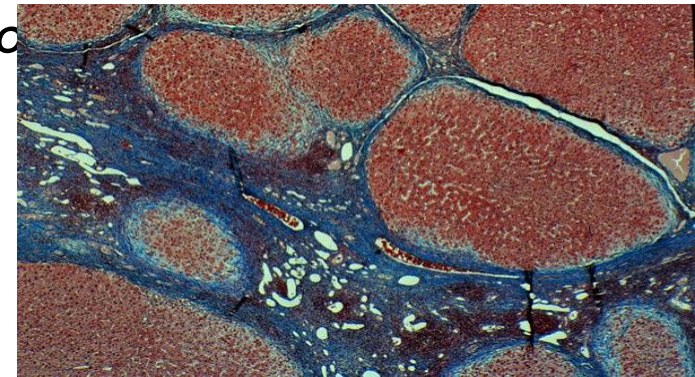
* With advanced disease



DIAGNOSIS CONFIRMATION?

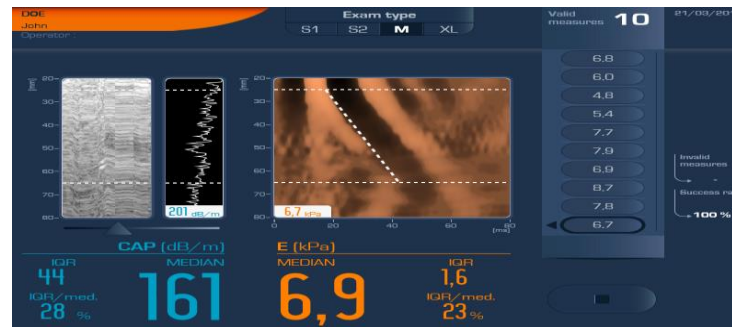
To confirm and support the clinical and radiologic diagnosis, a biopsy is often needed

1-Biopsy (histology)



2-Noninvasive tests

- ❑ Serum score systems
- ❑ Elastography (e.g fibroscan)



HOW TO ASSES SEVERITY & PROGNOSIS?

❑ **Child–Turcotte–Pugh score or Child Criteria (CPT score)...see table**

❑ MELD score

(model for end-stage liver disease)

- $\text{MELD} = 3.8[\text{serum bilirubin (mg/dL)}] + 11.2[\text{INR}] + 9.6[\text{serum creatinine (mg/dL)}] + 6.4$

❑ 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 INR	<4	4 to 6	>6
	<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

