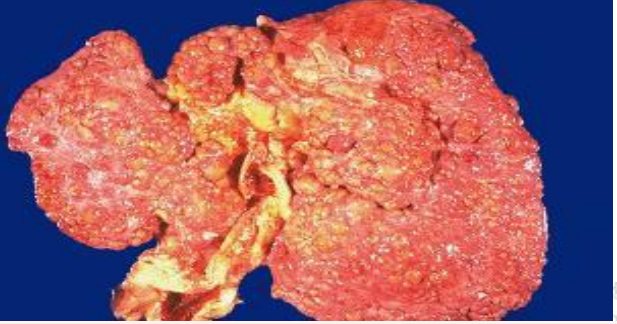

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LIVER CIRRHOSIS AND ITS COMPLICATIONS

MED341

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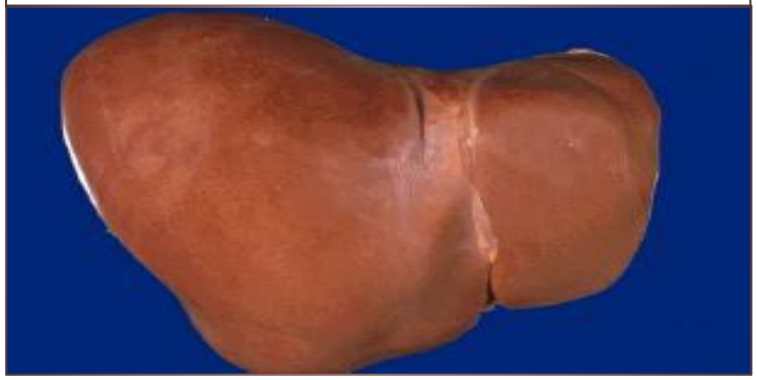
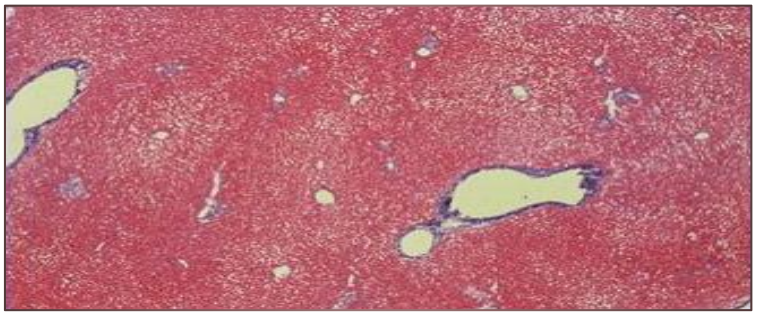
OBJECTIVES

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

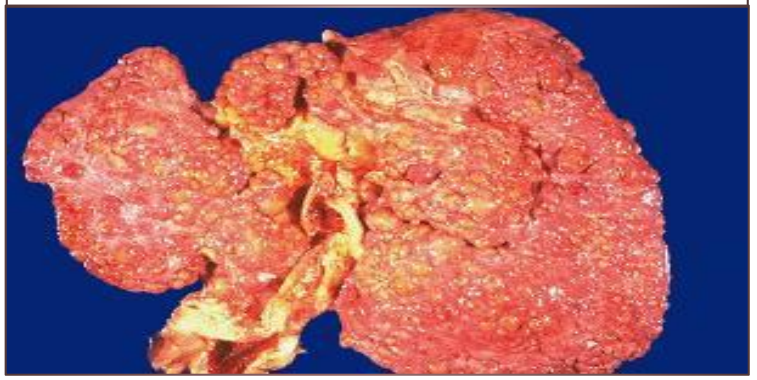
CIRRHOSIS: Late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules.

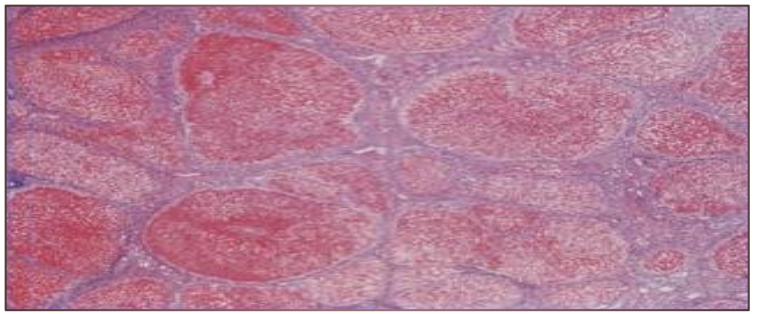
NORMAL LIVER





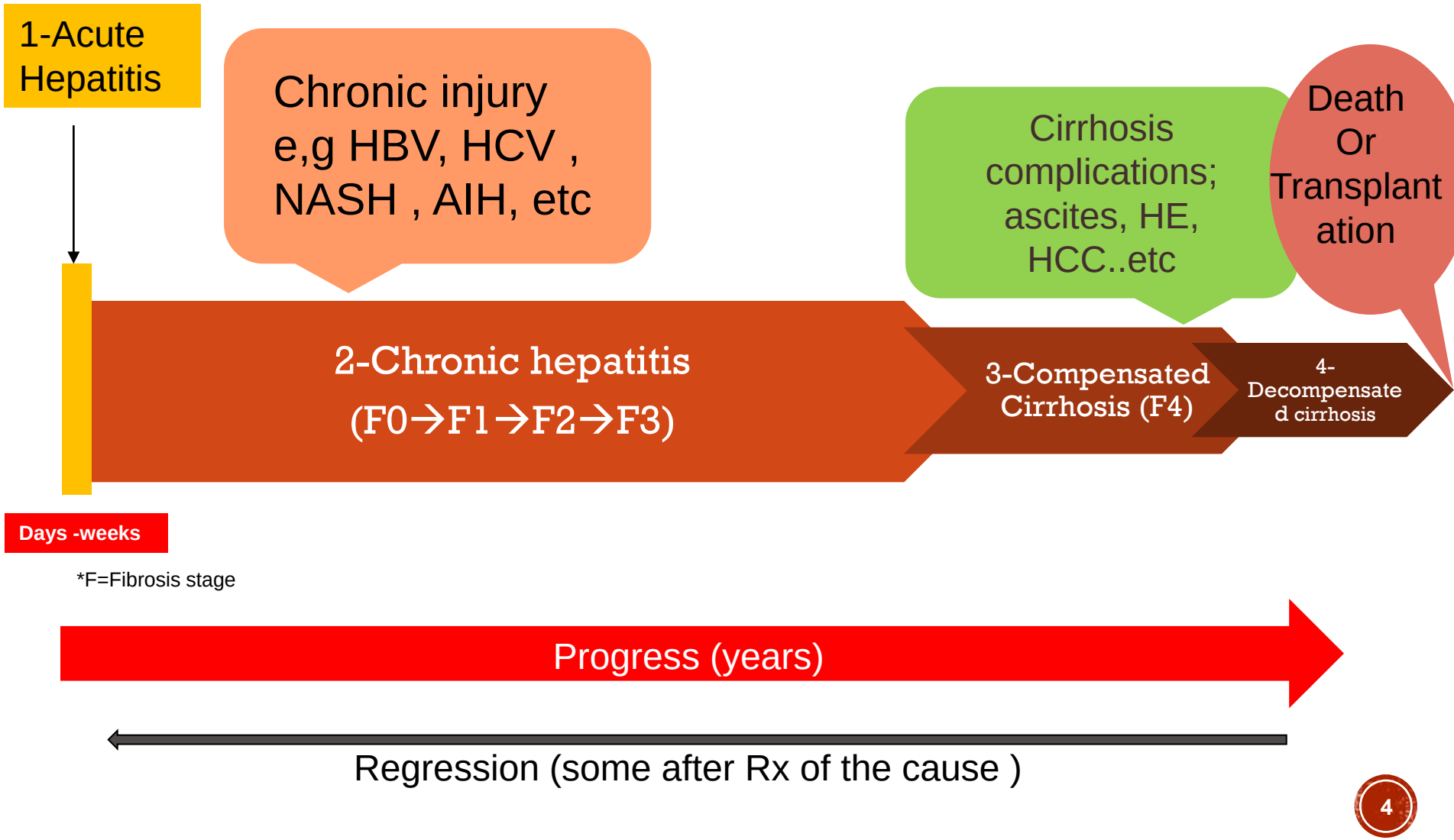
CIRRHOTIC LIVER





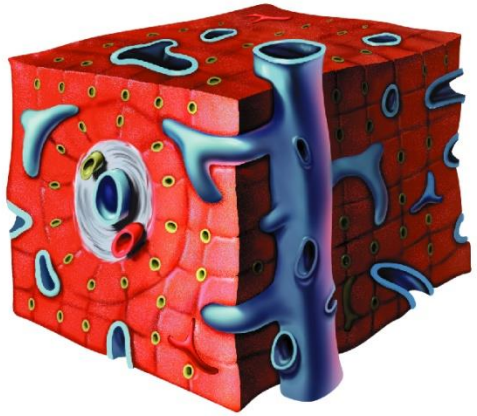
- The final stage of any chronic liver inflammation with fibrosis.
- Irreversible in its advanced stages, can be reversed in some if underlying cause is treated earlier.

SPECTRUM OF LIVER DISEASE

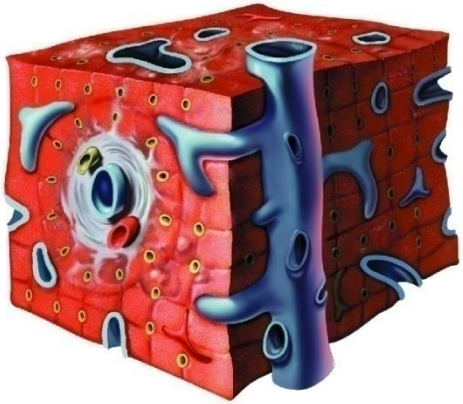


HISTOLOGIC STAGING

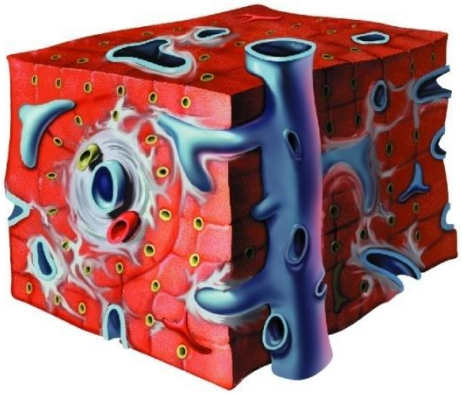
Stage 0



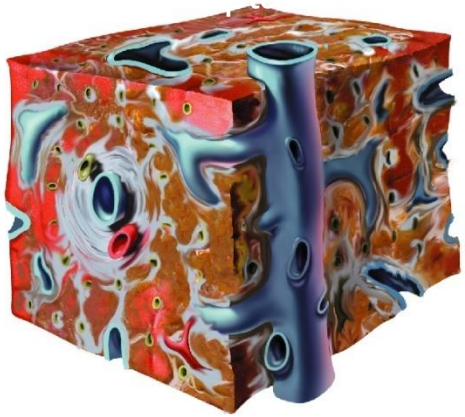
Stage 1



Stage 2



Stage 3



Stage 4

CAUSES OF CIRRHOSIS(=CHRONIC HEPATITIS)

Commonest

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

Remember! Some of these causes can cause acute hepatitis or acute on top of chronic

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

Other causes

- Autoimmune

(AIH, PBC, PSC)

- Metabolic & Hereditary

WD, A1AT, HH

- Vascular

BCS, HF

- Biliary

SC

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

PORTAL HYPERTENSION DEVELOPMENT

Portal hypertension is the beginning and requirement for most the cirrhosis complications

Intrahepatic

Cirrhosis

1-Structural changes

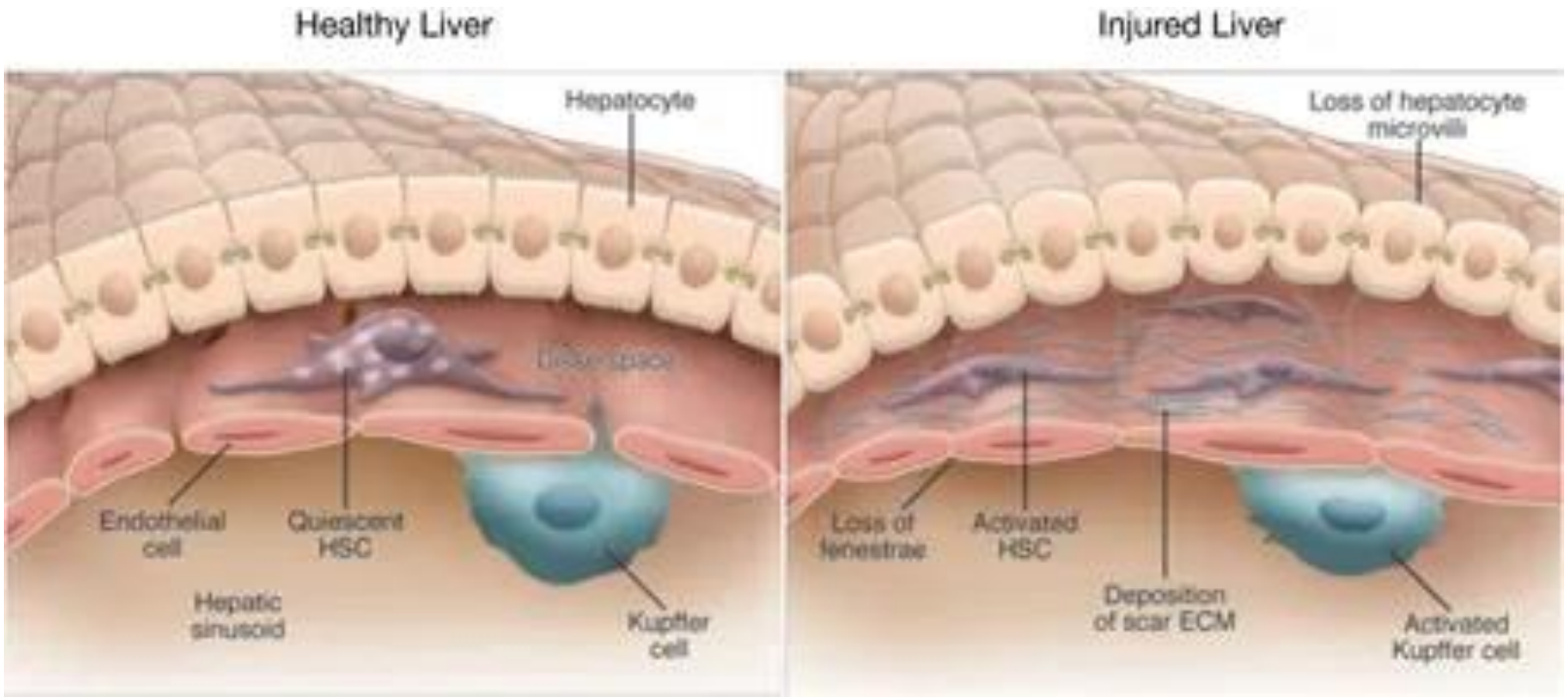
Distortion of the liver microcirculation by:
-fibrous septa, nodules, angiogenesis, and microthrombivascular occlusion

2-Dynamic changes

Intrahepatic cytokine-induced vasoconstriction and stellate cell contraction.

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

Møller S et al .Scand J Gastroenterol. 2015

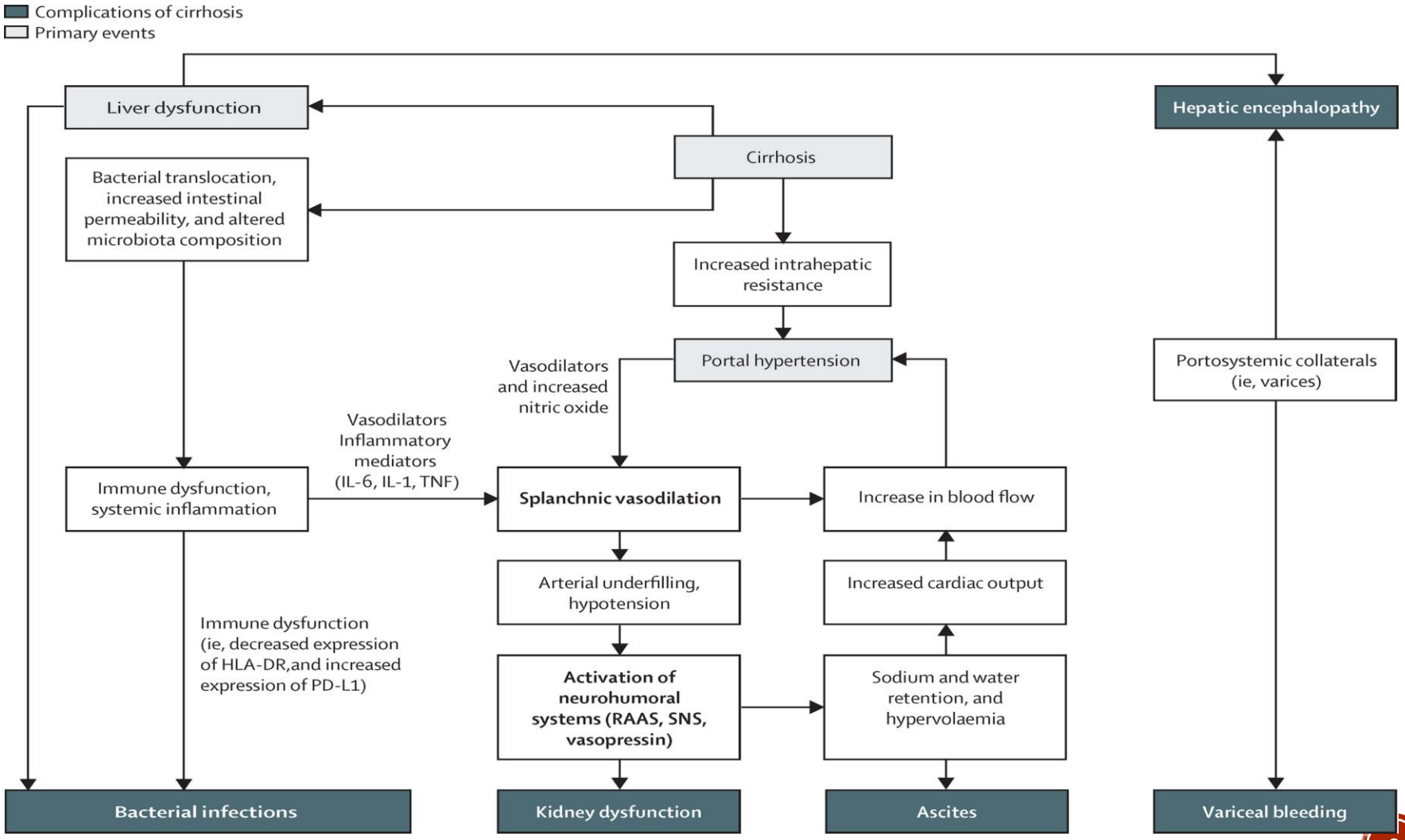


In healthy liver, hepatic stellate cells are kept quiescent and their main function is to store vitamin A droplets

When the liver is injured, hepatic stellate cells transform into activated myofibroblast-like cells to generate scar tissue

The Journal of Clinical Investigation 117(3): 539-548).

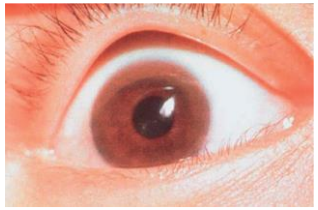
PATHOPHYSIOLOGY OF CIRRHOSIS COMPLICATIONS DEVELOPMENT

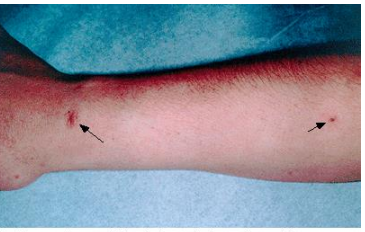


COMMON CIRRHOSIS COMPLICATIONS

- Ascites (Commonest)
  - Ascites +- refractory ascites
  - Spontaneous Bacterial Peritonitis
  - Hepatorenal syndrome
- Variceal hemorrhage *(separate lecture) the 2nd common*
- Hepatic Encephalopathy
- Bacterial infections
- Pulmonary
  - Hepatic hydrothorax (similar to ascites)
  - Hepatopulmonary syndrome
  - Portopulmonary HTN
- Hepatocellular carcinoma
- Frailty and sarcopenia
- Portal vein thrombosis
- Cirrhotic cardiomyopathy

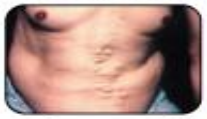
*Once a patients develop complications of cirrhosis, they are considered to have **Decompensated Cirrhosis***



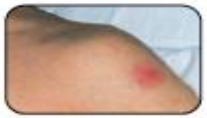


Spider angiomas This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left. 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

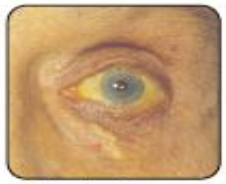


Gynaecomastia



Spider naevi

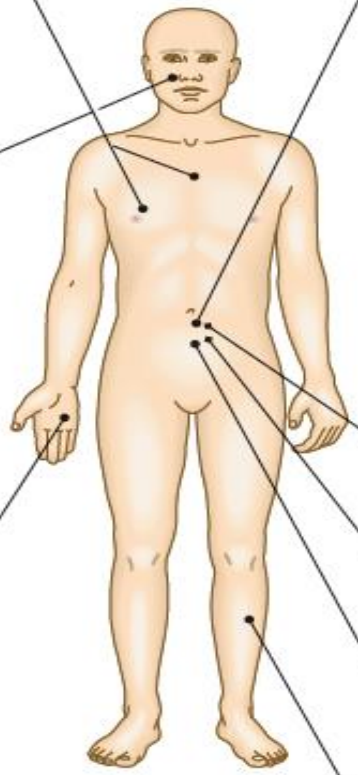
2 Face
Jaundice
Spider naevi
Parotid swelling
Rhinophyma



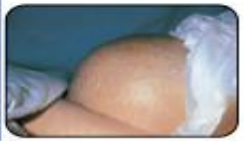
Xanthelasma and jaundiced sclera in a patient with chronic cholestasis

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

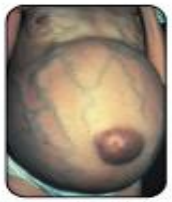
Palmar erythema



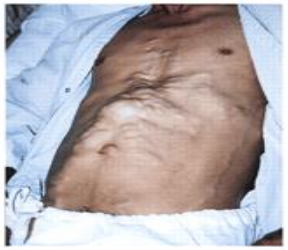
4 Abdomen: inspection
Scars
Distension
Movement
Veins
Testicular atrophy



Abdominal swelling in ascites



Dilated abdominal wall veins (caput medusae)



5 Abdomen: palpation
Hepatomegaly
Splenomegay

6 Abdomen: percussion
Ascites

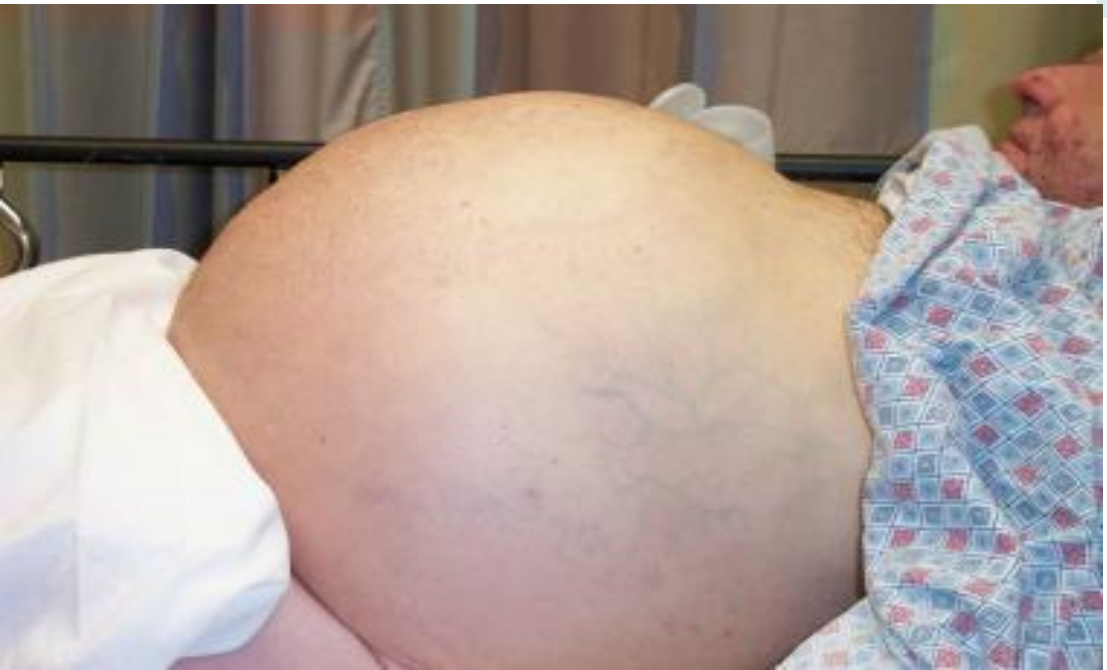
7 Abdomen: auscultation
Bowel sounds
Hepatic bruit

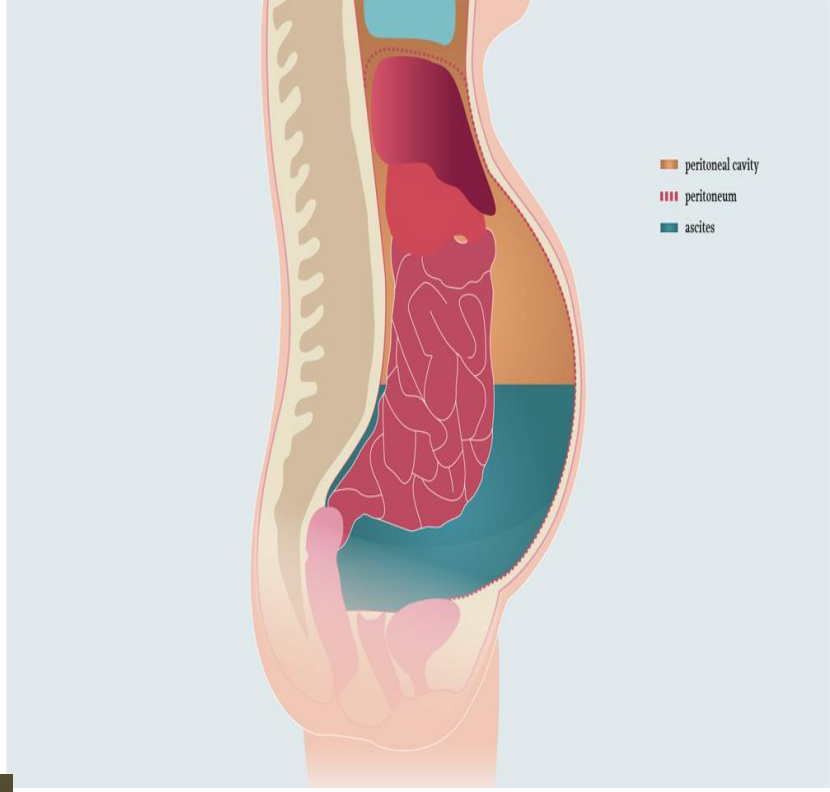
8 Legs
Bruising
Oedema

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

Ascites is graded as:

Grade 1 (mild) ascites, which is only detected on ultrasonography

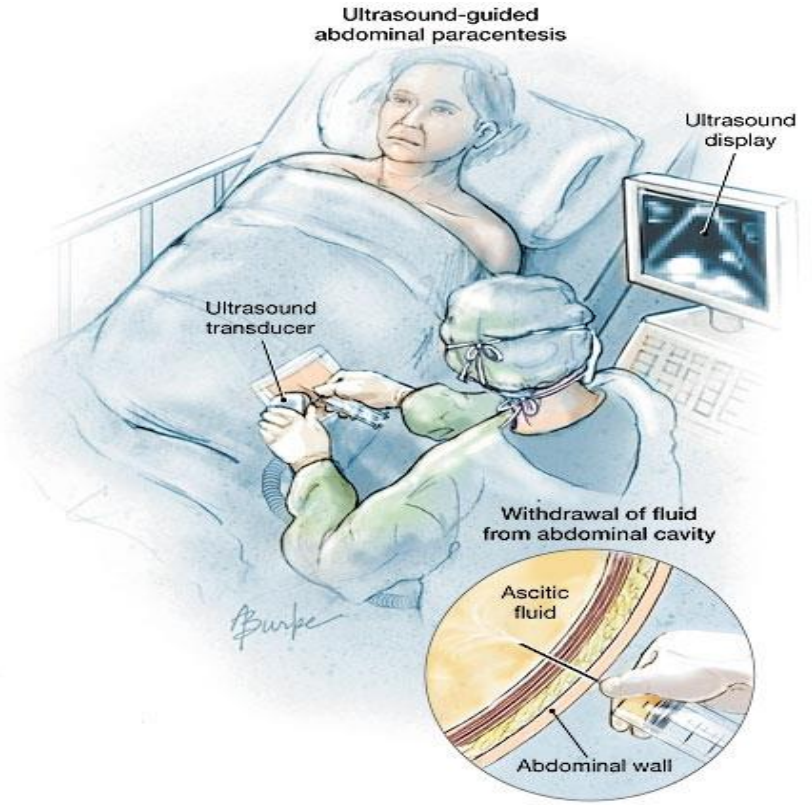
Grade 2 (moderate) ascites, characterized by moderate abdominal distension, discomfort, and shifting dullness

Grade 3 (severe) ascites, which manifests as tense abdominal distension with a fluid wave (Thrill).

DIAGNOSTIC PARACENTESIS

Diagnostic paracentesis should be done for any clinically detectable ascites (grade2, 3):

- Any new ascites should be tapped and analyzed!
- All patients hospitalised for cirrhosis with ascites or other complications of cirrhosis (to rule out the presence of spontaneous bacterial peritonitis).



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)	Low SAAG <1.1 g/dL (11 g/L)
Portal hypertension related	Non-portal hypertension related
▪ Cirrhosis ▪ Heart failure/constrictive pericarditis ▪ Alcoholic hepattis ▪ Budd chiari ▪ Massive hepatic metastases	▪ Peritoneal carcinomatosis ▪ Peritoneal tuberculosis ▪ Secondary peritonitis ▪ Pancreatitis ▪ Serositis ▪ Nephrotic syndrome

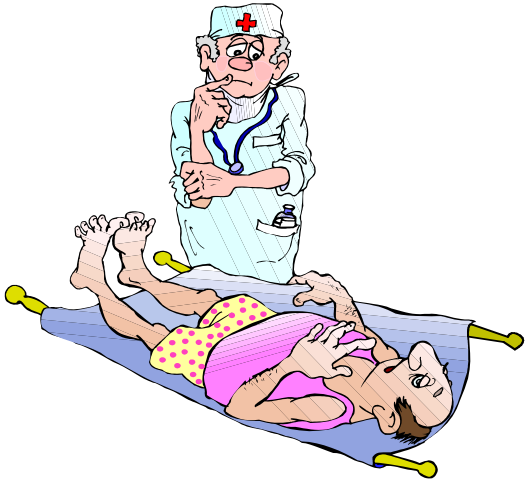
INITIAL TREATMENT OF ASCITES

- **1-Dietary sodium restriction**
  - A moderate restriction of sodium intake (80–120 mmol/ day, corresponding to 4.6–6.9 g of salt)

  =This is generally equivalent to a no added salt diet with avoidance of pre-prepared meals.
- **2-Diuretics:** anti-mineralocorticoid (e.g Spironolactone) alone or with loop diuretics(Furosemide)
  - Monitor electrolytes and kidney function.

- Avoid some drugs: Non-steroidal anti-inflammatory drugs, Angiotensin-converting-enzyme inhibitors, angiotensin-II antagonists, or a1-adrenergic receptor blockers, aminoglycosides
- Rx of underlying cause
- Evaluation for liver transplantation (this is applied as well, for any patients with cirrhosis complications)

REFRACTORY ASCITES



- ~10%

Defined as ascites that:

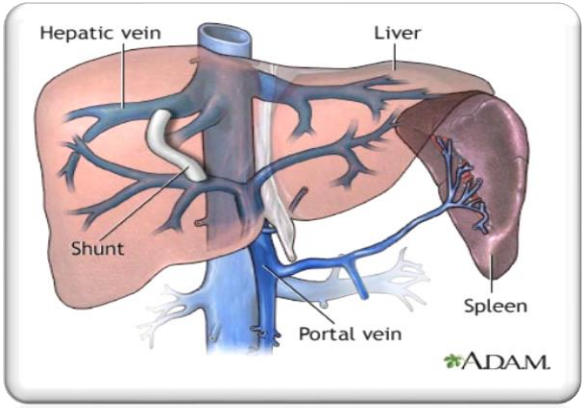
- Unresponsive to sodium-restricted diet and high dose diuretic treatment

Or

- Development of clinically significant complications of diuretics

MANAGEMENT LINES REFRACTORY ASCITES

1. Large Volume Paracentesis +add albumin (if draining> 5 L of fluid).
2. Trans-jugular intrahepatic portosystemic shunt (TIPS)
3. Liver transplantation



SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Defined as a bacterial infection of the ascitic fluid, without any identifiable, intra-abdominal, surgically treatable source of infection.

- The diagnosis is established by
  - PMN count (>250 cells/mm3)
  - Positive culture is not required for diagnosis (<50% positive), but needed to guide antibiotic therapy
- Organisms

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

  -sometimes others: streptococcal, staphylococcal , enterococcus infections.

Clinical manifestations: (Variable, sometimes asymptomatic)

- Sometimes
  - Fever
  - Abdominal pain/tenderness
  - Altered mental status

In-hospital mortality remains at approximately 20%

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:**

   (1.5 g/kg at diagnosis and 1 g/kg on day 3) is recommended in patients with SBP

BACTERIAL INFECTIONS

- Cirrhosis patients have a risk of sepsis 2-6 times higher than other patients

What infections?

- SBP
- Urinary tract infection
- Other infections: pneumonia, soft tissue infections, and spontaneous bacteraemia are among the most common infections in cirrhosis.

- What's is the impact?:
  - Associated with development of other cirrhosis complications such as H. encephalopathy, variceal bleeding, kidney injury , more liver dysfunction. Etc
  - Frequent admissions
  - Higher morbidity and mortality

PRESENTATION OF INFECTION IN CIRRHOSIS

- Not always specific
- Sometime only some of the following features:
  - Signs of systemic inflammation (ie, fever, high white blood cell count, high C-reactive protein, and tachycardia)
  - Worsening liver function; hepatic encephalopathy; acute kidney injury; gastrointestinal bleeding; or shock.
- Therefore; bacterial infections should be ruled out in all patients presenting with complications of cirrhosis or worsening of liver or kidney function

ACUTE KIDNEY INJURY-HEPATORENAL SYNDROME (HRS)

-Acute kidney injury is prevalent in up to 30–50% of hospitalised patients with decompensated cirrhosis

Precipitating factors acute kidney injury in cirrhosis: (commonest)

- Bacterial infections
- Diuretic overdose
- Gastrointestinal bleeding
- Nephrotoxic drugs (eg, non-steroidal anti-inflammatory drugs)
- Others….

- Patients with cirrhosis can present with acute kidney injury due to a variety of causes: prerenal, hepatorenal syndrome, intrinsic, or postrenal acute kidney injury.
- Prerenal acute kidney injury is the most frequent cause of acute kidney injury in hospitalised patients with cirrhosis

ACUTE KIDNEY INJURY-HEPATORENAL SYNDROME (HRS)

-Acute kidney injury–hepatorenal syndrome is a unique form of functional kidney failure that develops in patients with advanced cirrhosis.

Require the presence of cirrhosis and ascites

- Dx by exclusion (NB: most common cause of acute renal failure in cirrhosis is pre-renal not HRS)

- Rx
  - Correct underlying cause
  - Albumin+Vasoconstrictors (Terlipression, or octeriotide, or midodrine, epinephrine)
  - Hemodialysis
  - Liver transplantation.

HEPATIC HYDROTHORAX

- Pleural effusion in a patient with cirrhosis in the absence of cardiac, pulmonary, or pleural disease.
- Commonly Rt side
- 5-10% of cirrhosis patients.
- Cause: movement of ascitic fluid into the pleural space through defects in the diaphragm.

- Dx
  - High SAAG
  - Transudative fluid

- Management similar to ascites, thoracentesis may be required for diagnosis, or therapeutic.

HEPATOPULMONARY SYNDROME (HPS)

Arterial hypoxaemia in patients with cirrhosis and portal hypertension secondary to intrapulmonary vascular dilatation or shunting

Dx :

-Contrast(Microbubble) echocardiography

-Lung perfusion scan

Rx:

-O2 Supportive therapy

-Liver transplantation

PORTOPULMONARY HTN

- Pulmonary hypertension in patient with portal hypertension in the absence of other causes of pulmonary artery or venous hypertension. namely: chronic thromboembolism, chronic lung disease/hypoxia; chronic left heart disease.
- Not common

- Patients may be asymptomatic but often present with exertional dyspnoea and they may have clinical signs of right heart failure when moderate to severe disease develops.
- Diagnosis:
  - Suggested by echocardiography
  - Confirmed by right heart catheterization

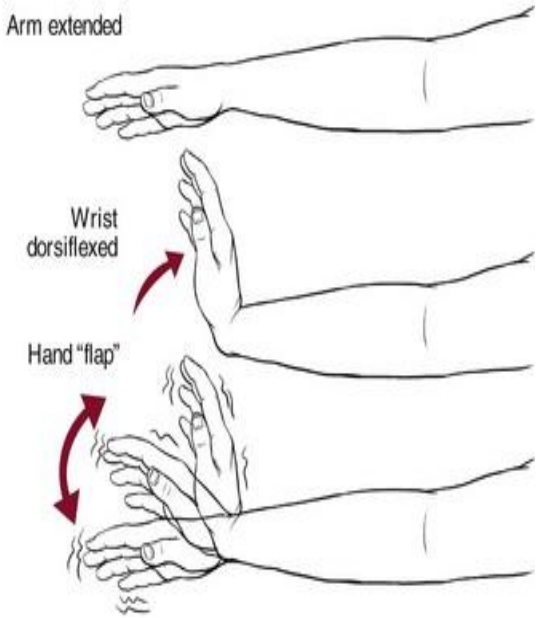
HEPATIC ENCEPHALOPATHY (HE)

DEFINITION OF HE

- HE 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.

Grades of Hepatic Encephalopathy (West Haven Criteria)		
Covert	**Grade 1**	Inattention, euphoria/ anxiety, **altered sleep pattern**, ↓attention span
Overt	**Grade 2**	Lethargy, behavior Δs, time disorientation, **asterixis**, personality Δs, hypoactive DTRs
	Grade 3	**Somnolence** to semistupor, responsive to stimuli, time & place disorientation, asterixis, hyperactive DTRs
	Grade 4	**Coma**



PATHOPHYSIOLOGY OF HE

Different mechanisms

- Neurotoxin (ammonia)
- Blood-to-brain transport of neurotransmitter
- Sepsis, neuroinflammation, and alterations in gut flora appear to be additional factors.

<u>Broadley 2 major pathophysiologic changes:</u>

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

---------->>>> **<u>enhanced neural inhibition</u>**

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**

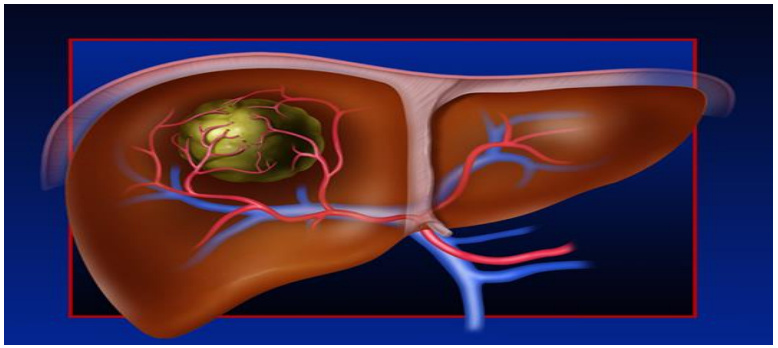
RX

1. Identify and treat precipitating factors for HE

2. Measures to lower the blood ammonia concentration

   - Non-absorbable disaccharides (lactulose or lactitol)are the first choice for treatment

   - Other medications:
     - Rifaximin (nonabsorbable oral antibiotic)
     - Others.



HEPATOCELLULAR CARCINOMA (HCC)

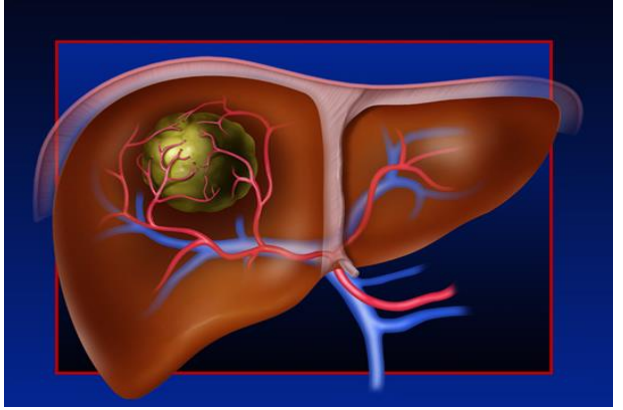
- Patients with cirrhosis have a markedly increased risk of developing HCC.

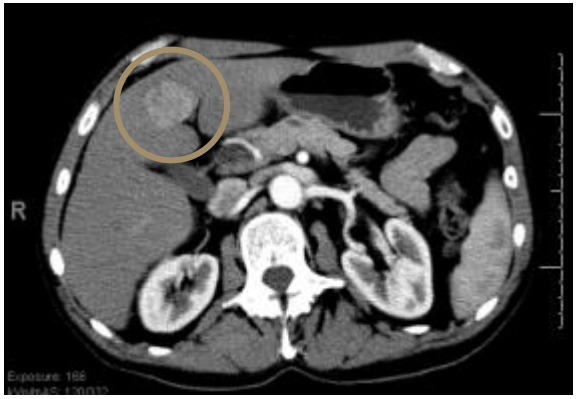
- Incidence in compensated cirrhosis is ~3%/year
- 25-30% in 10 y.

TESTS TO DIAGNOSE HCC

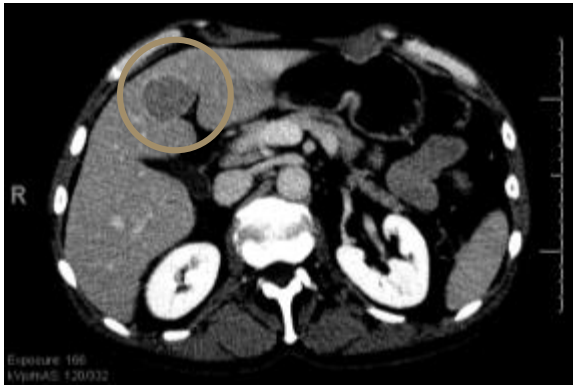
- Radiology (most important)
- Biopsy
- Blood tests: alphafetoprotein (AFP) high in some patients

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, liver and patients status)

- 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
- High survival rate after transplantation
- Depends upon the severity of disease and the absence of contraindications.
- Source of liver: donor (living related) or deceased.

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?

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- Symptoms
- Signs
- Lab and imaging
- Management

CLINICAL MANIFESTATIONS

- **No symptoms (Most patients in compensated 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.

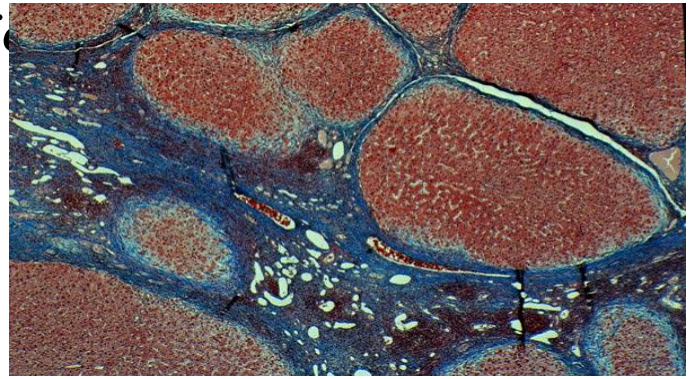
INVESTIGATIONS IN CIRRHOSIS

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	Cirrhosis complications:
Anemia	• Ascites*
Low serum albumin*	• Hepatocellular carcinoma*
Prolonged prothrombin time/elevated INR*	• Portal/splenic/superior mesenteric vein thrombosis*
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