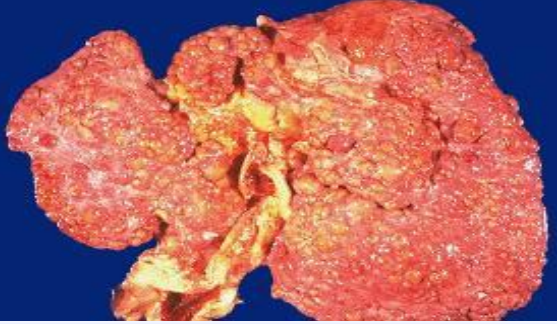

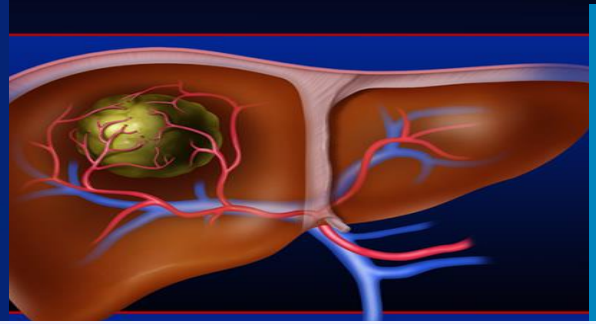

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King Saud University
1957

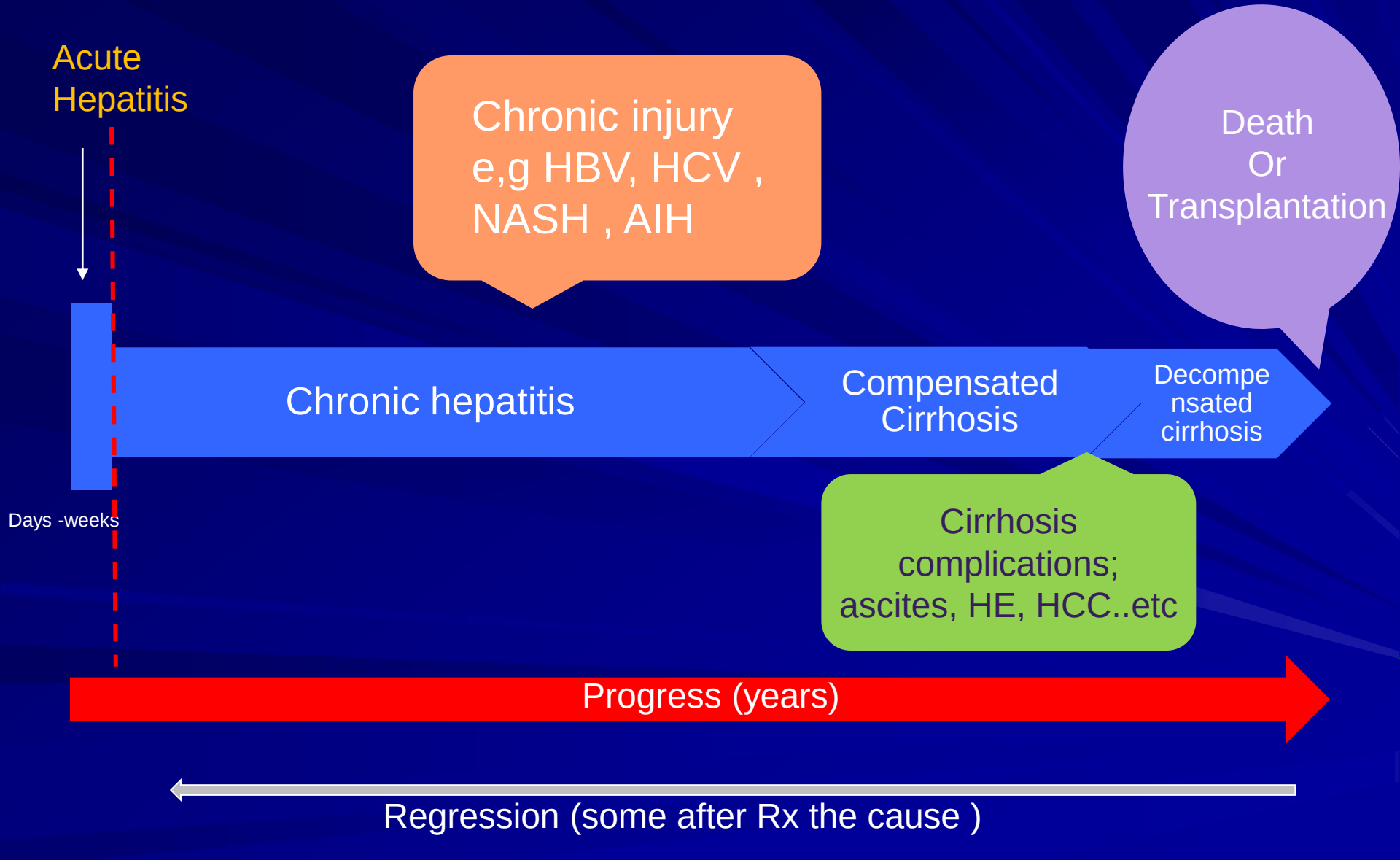
Approach To Chronic Liver Disease

Khalid Alswat, MD, MRCP, FACP
Associate Professor, Consultant Gastroenterologist/hepatologist
College of Medicine, King Saud University

Objectives

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

Spectrum of Liver Inflammation



Causes of Cirrhosis

Commonest

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

Other causes

- Autoimmune

(AIH, PBC, PSC)

- Metabolic & Hereditary

WD, A1AT, HH

- Vascular

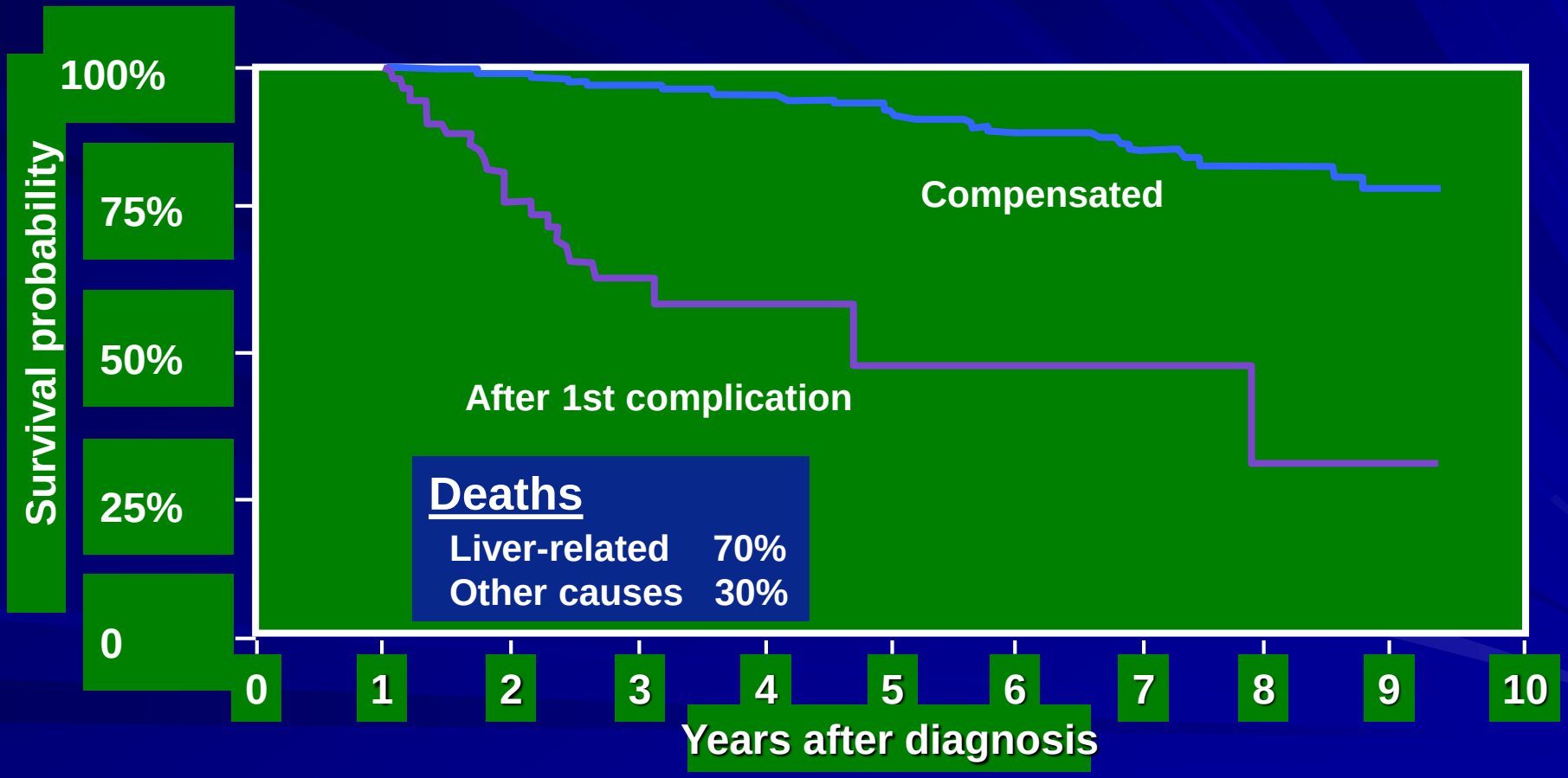
BCS, HF

- Biliary

SC

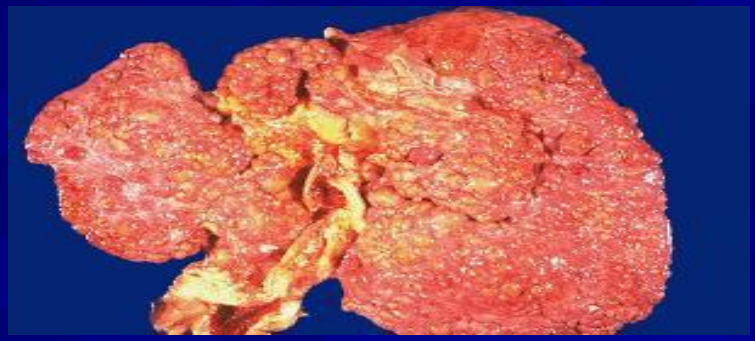
- Drugs

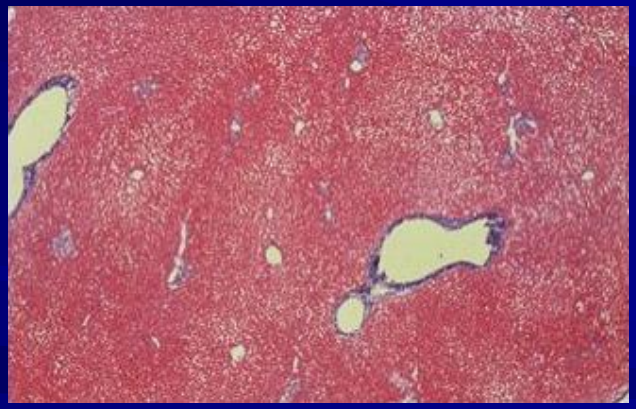
Natural History of HCV Cirrhosis

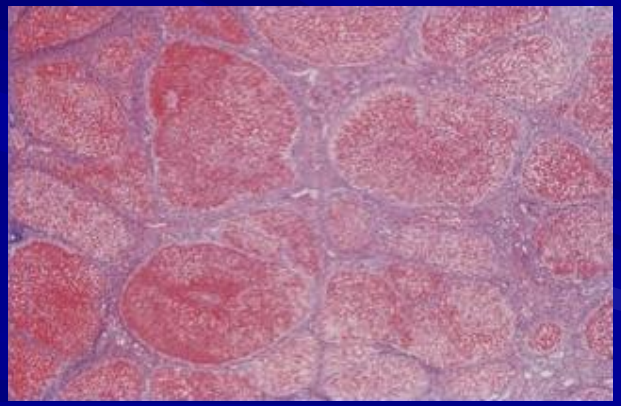


Adapted from Fattovich G et al. Gastroenterology. 1997;112:466-467.

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

Pathophysiology

- Chronic injury of the hepatic parenchyma
- Extensive fibrosis - distortion of the hepatic architecture
- Formation of regenerative nodules
- Portal hypertension
- Vascular and humoral changes

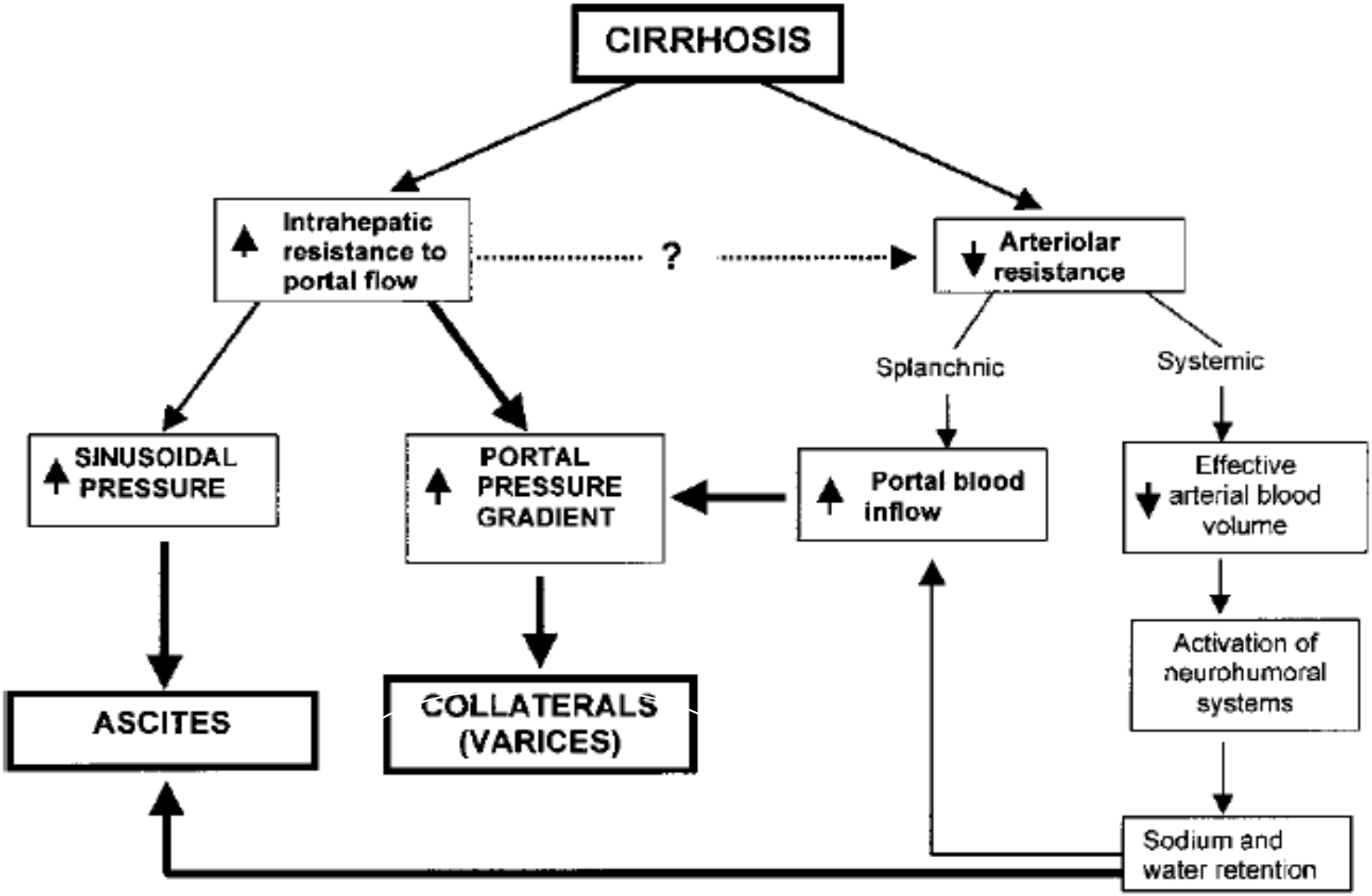


Figure 1. Pathogenesis of portal hypertension and its two main complications: varices and ascites.

How to approach patient with Cirrhosis?

- Symptoms
- Signs
- Lab
- Management

Clinical manifestations

- No symptoms (Most patients in early cirrhosis)

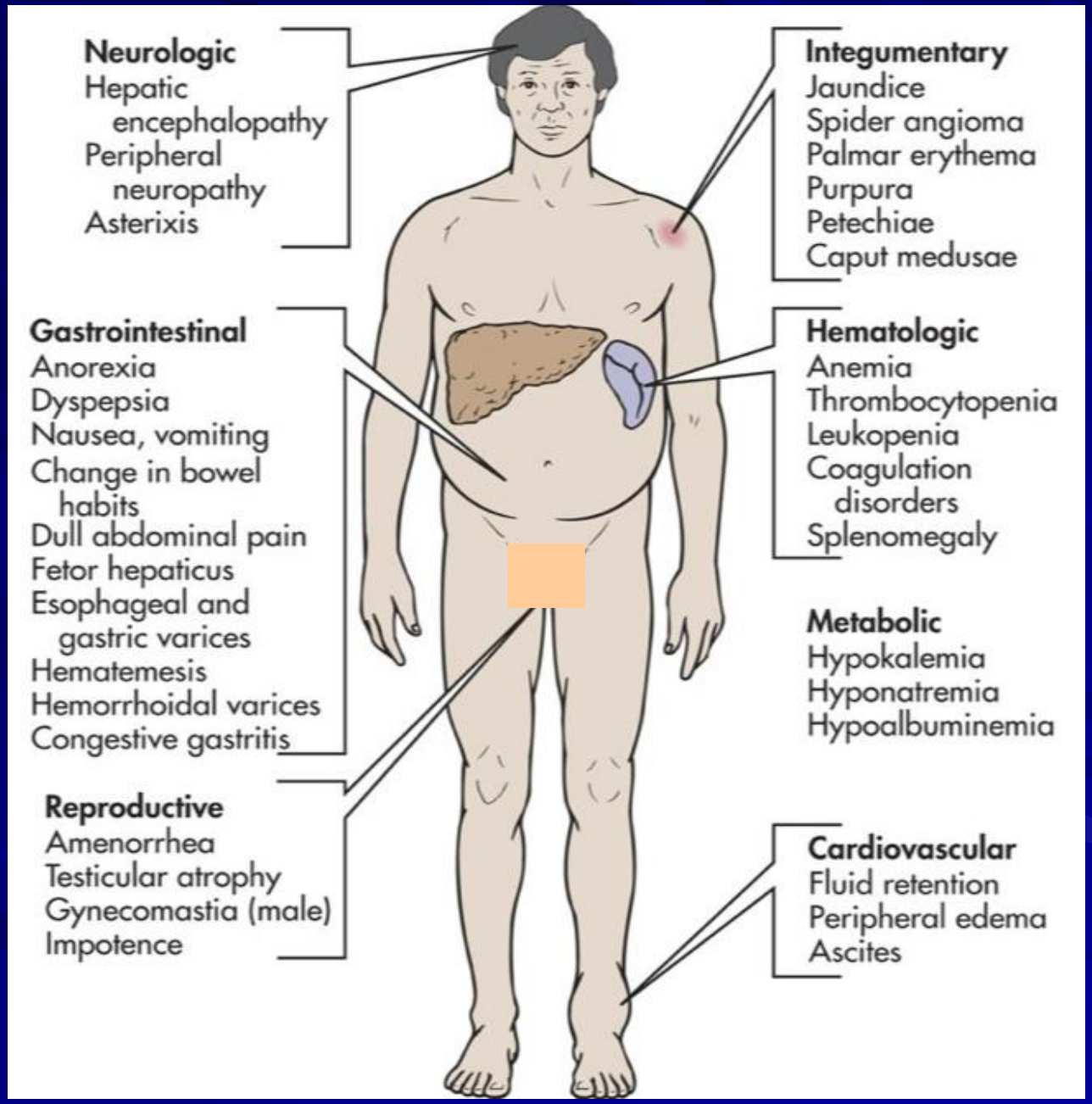
- Symptoms of cirrhosis (sometimes non-specific sx)
- Symptoms of decompensations (when liver start to fail.)

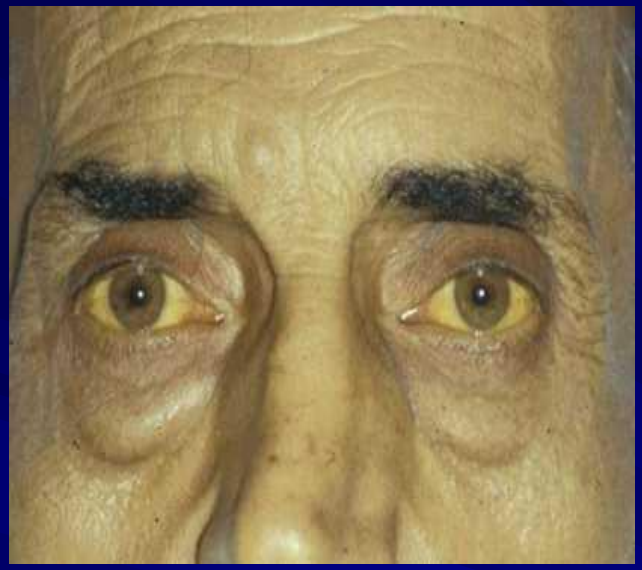
History

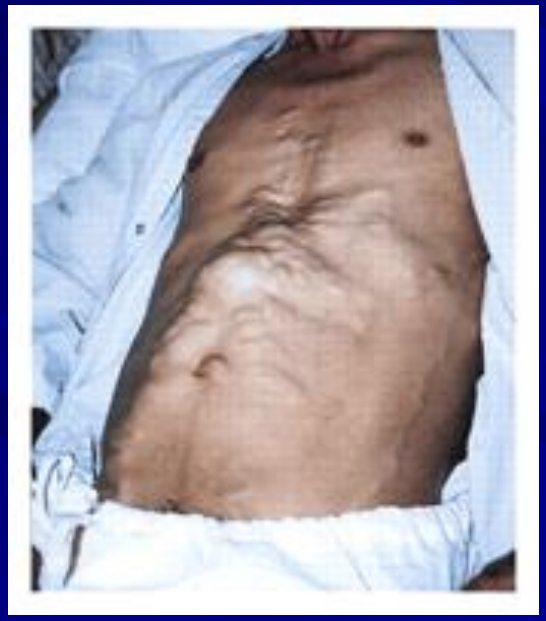
Presenting symptoms	Past and drug History	Family history	Social history
1-Asymptomatic 2-Nonspecific constitutional symptoms, such as fatigue, weakness, and weight loss, etc.) 3-Symptoms of decompensation -abdominal distension due to ascites and hepatomegaly, -coffee-ground vomitus and black stool (melena) 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

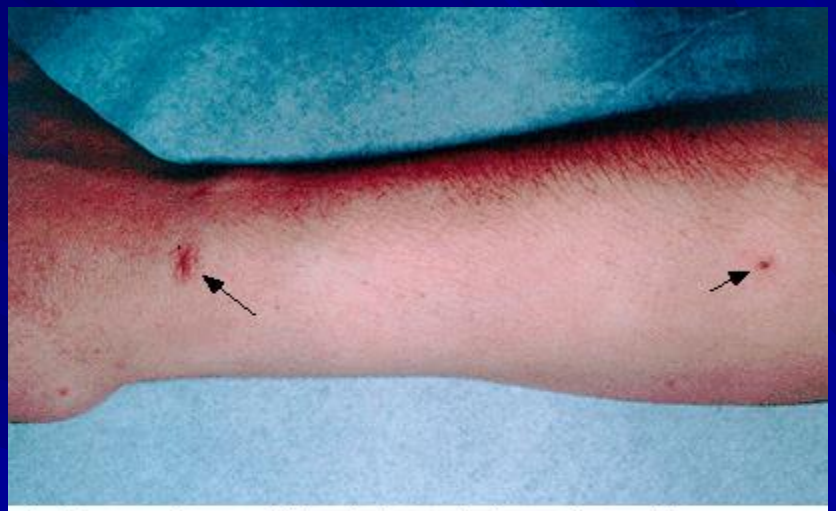
Clinical Features

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.


Neurologic
Hepatic encephalopathy
Peripheral neuropathy
Asterixis
Integumentary
Jaundice
Spider angioma
Palmar erythema
Purpura
Petechiae
Caput medusae
Gastrointestinal
Anorexia
Dyspepsia
Nausea, vomiting
Change in bowel habits
Dull abdominal pain
Fetor hepaticus
Esophageal and gastric varices
Hematemesis
Hemorrhoidal varices
Congestive gastritis
Hematologic
Anemia
Thrombocytopenia
Leukopenia
Coagulation disorders
Splenomegaly
Metabolic
Hypokalemia
Hyponatremia
Hypoalbuminemia
Reproductive
Amenorrhea
Testicular atrophy
Gynecomastia (male)
Impotence
Cardiovascular
Fluid retention
Peripheral edema
Ascites





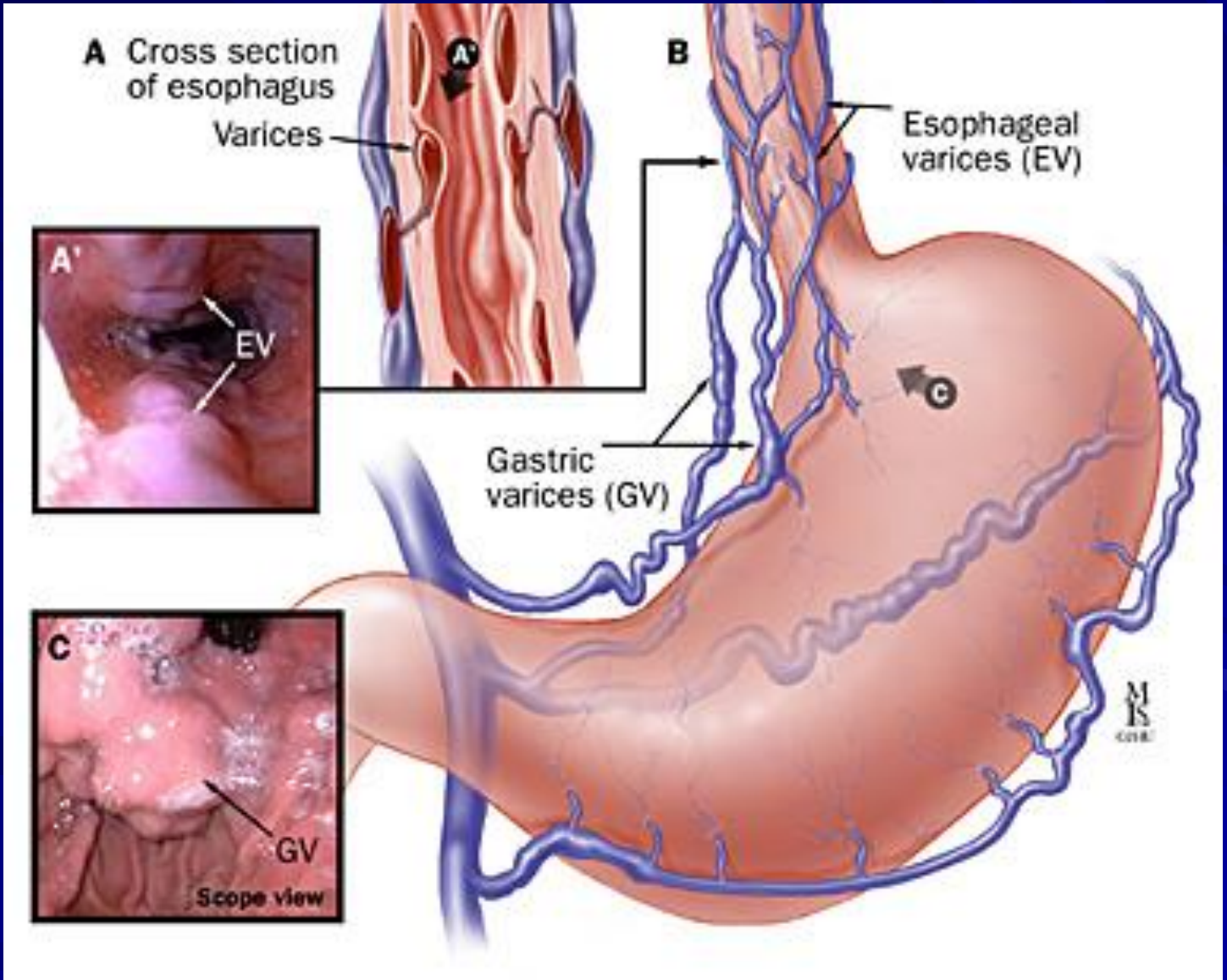


Spider angiomas This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left.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

Common Cirrhosis Complications

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

Portal hypertension



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*	

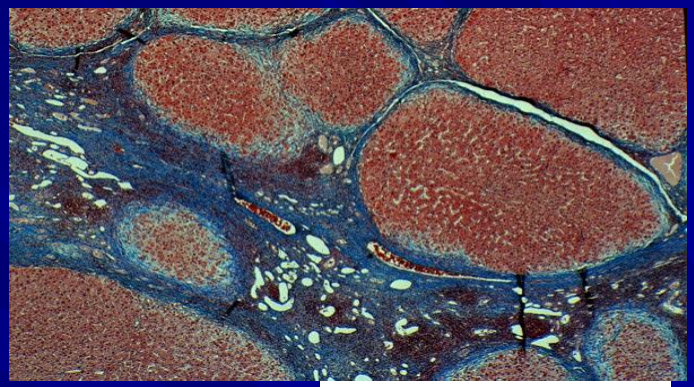
* With advanced disease

Important Diagnostic Tests in Common Liver Diseases

Disease	Diagnostic Test
Hepatitis A (acute)	Anti-HAV IgM
Hepatitis B	
Acute	HBsAg and anti-HBc IgM
Chronic	HBsAg and HBeAg and/or HBV DNA
Hepatitis C	Anti-HCV and HCV RNA
Hepatitis D (delta)	HBsAg and anti-HDV
Hepatitis E (acute)	Anti-HEV IgM and HEV RNA
Autoimmune hepatitis	ANA or ASMA, LKM-ab, elevated IgG levels, and compatible histology
Primary biliary cholangitis	AMA, elevated IgM levels, and compatible histology
Primary sclerosing cholangitis	P-ANCA, cholangiography
Drug-induced liver disease	History of drug ingestion
Alcoholic liver disease	History of excessive alcohol intake and compatible histology
Nonalcoholic steatohepatitis	Ultrasound or CT evidence of fatty liver and compatible histology
α_1 Antitrypsin disease	Reduced α_{-1} antitrypsin levels, phenotype PiZZ or PiSZ
Wilson's disease	Decreased serum ceruloplasmin and increased urinary copper; increased hepatic copper level
Hemochromatosis	Elevated iron saturation and serum ferritin; genetic testing for *HFE* gene mutations
Hepatocellular cancer	Elevated α-fetoprotein level , CT or MRI with contrast

Diagnosis confirmation?

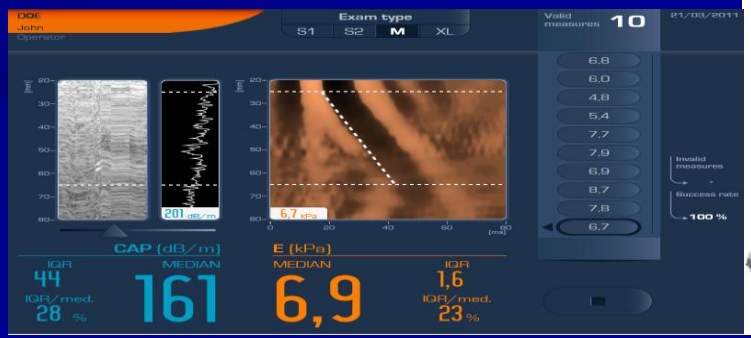
To confirm and support the clinical and radiologic manifestations if needed



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

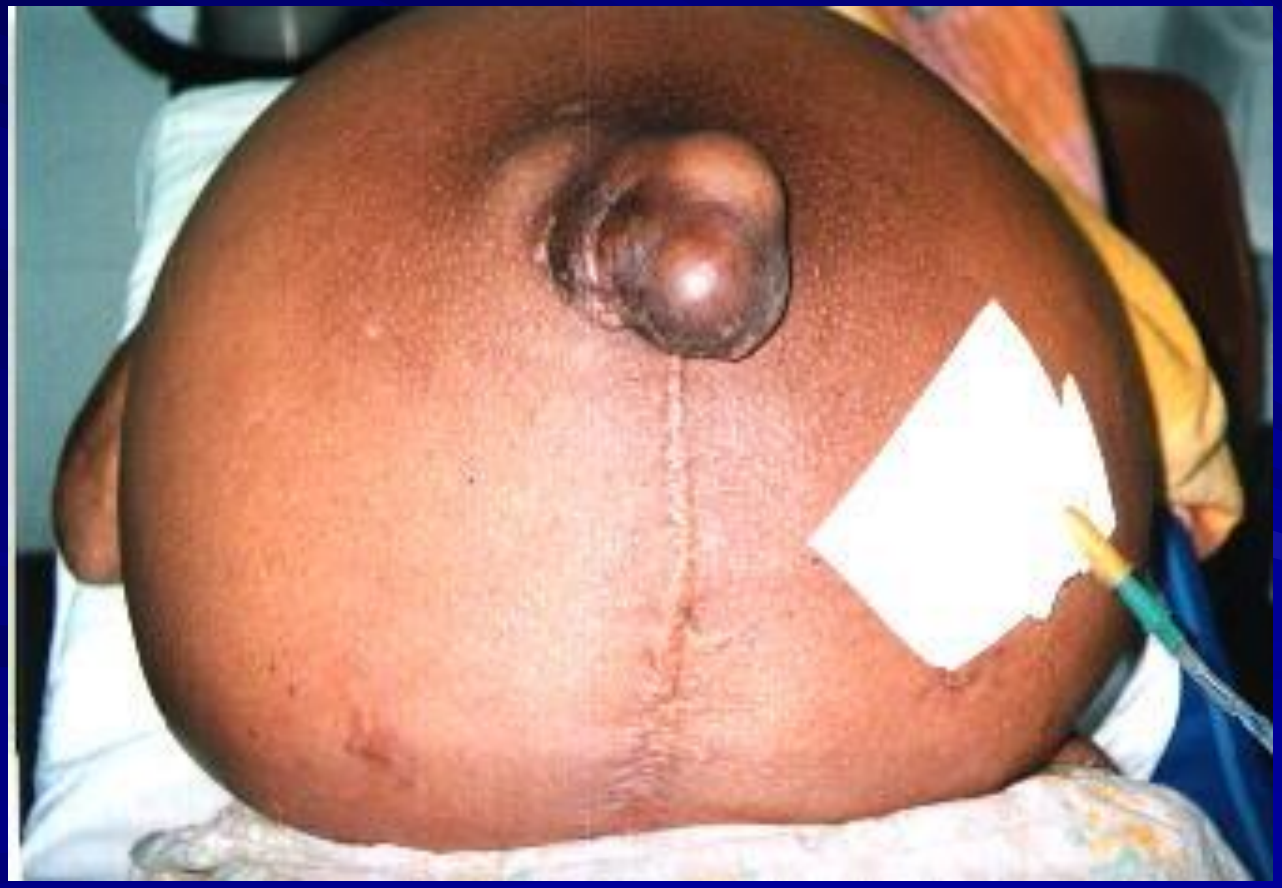
- others

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 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%

ASCITES



Ascites

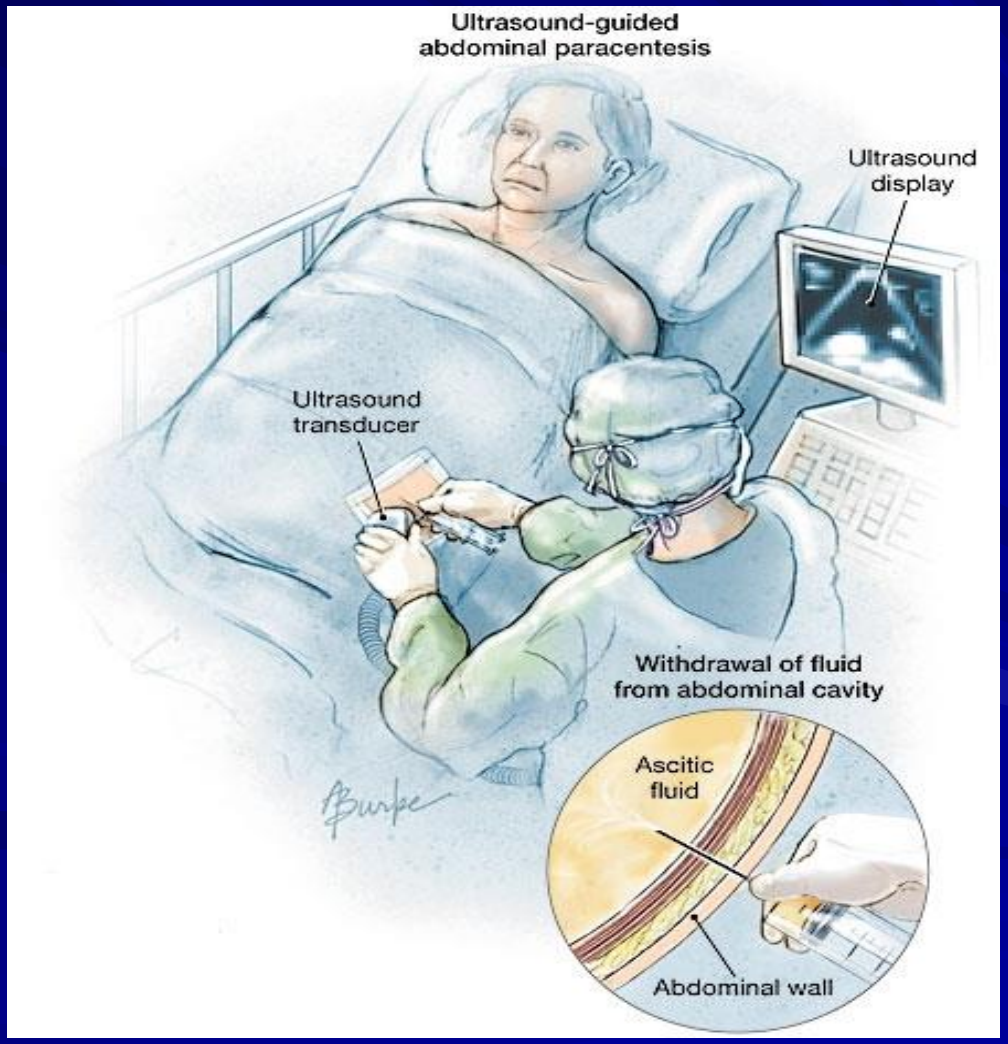
- Accumulation of fluid within the peritoneal cavity
- 1,500 mL of fluid must be present before flank dullness is detected.
- Shifting dullness: 83% sensitivity and 56% specificity in detecting ascites.
- If no flank dullness is present less likely ascites (< 10%).
- Ascites:
  1. 85% of due to cirrhosis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

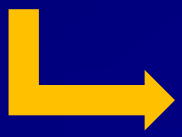
Any new ascites should be tapped and analyzed!



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.[17] 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 hepattis
- 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

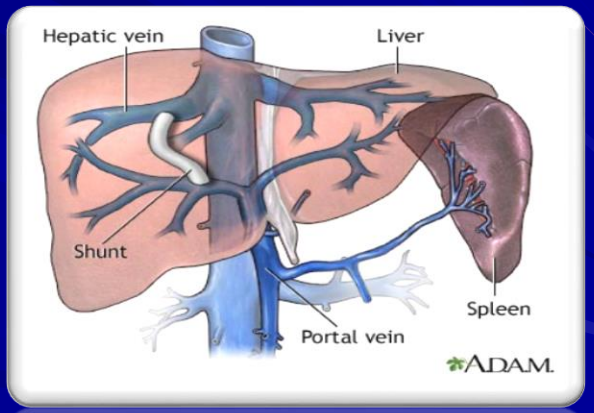
(400 mg per day of spironolactone and 160 mg per day furosemide), or

- Development of clinically significant complications of diuretics

, e.g., encephalopathy, serum creatinine greater than 2.0 mg/dL, serum sodium less than 120 mmol/L, or serum potassium greater than 6.0 mmol/L

Management Lines

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



Spontaneous Bacterial Peritonitis (SBP)

- Infection of ascitic fluid

-the 3 most common isolates: Escherichia coli, Klebsiella pneumoniae, and Streptococcal pneumoniae

- Clinical manifestations: (all, some, sometimes-none)
  - Fever
  - Abdominal pain
  - Abdominal tenderness
  - Altered mental status

SBP

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

Rx

- 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

- Albumin; when
  - creatinine >1 mg/dL
  - BUN >30 mg/dL
  - total bilirubin >4 mg/dL

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

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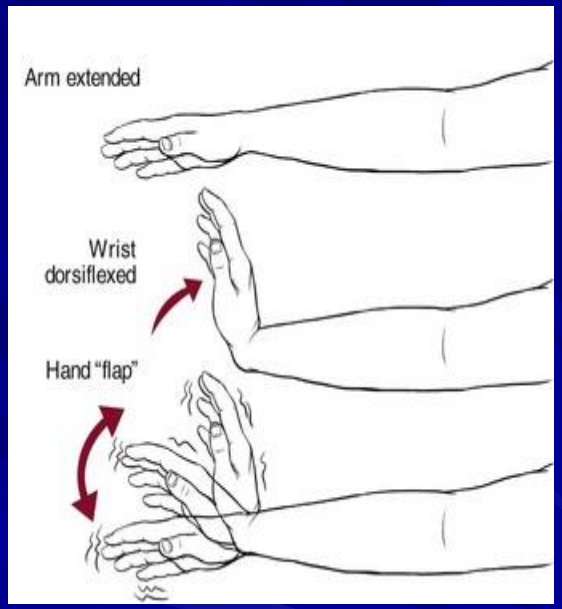


Pathophysiology of HE

Different mechanisms

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

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

- enhanced neural inhibition

Precipitants of hepatic encephalopathy in patients with cirrhosis

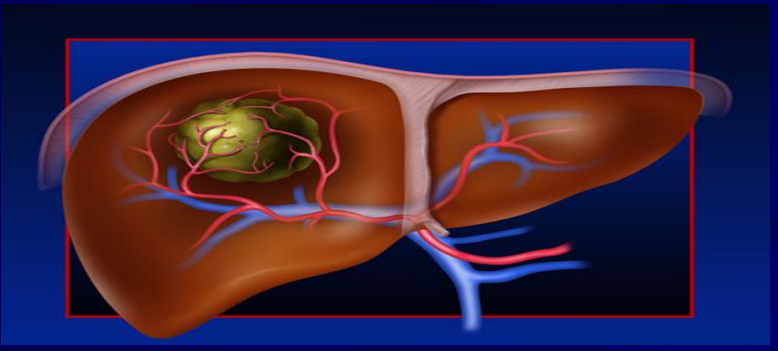
- **Drugs**
  - Benzodiazepines
  - Narcotics
  - Alcohol
- **Increased ammonia production, absorption or entry into the brain**
  - Excess dietary intake of protein
  - Gastrointestinal bleeding
  - Infection
  - Electrolyte disturbances such as hypokalemia
  - Constipation
  - Metabolic alkalosis
- **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

- Identify and treat precipitating factors for HE
- Lactulose is the first choice for treatment

- Other medications:

  Rifaximin, Metronidazole, Oral BCAAs and LOLA



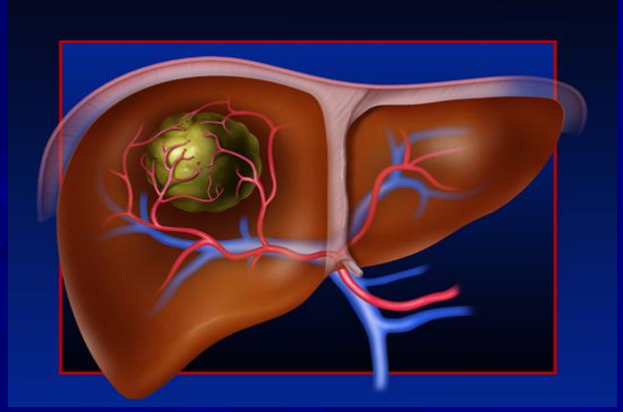
Hepatocellular Carcinoma (HCC)

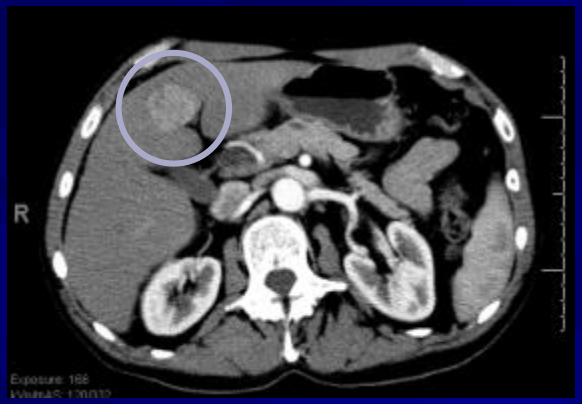
- Patients with cirrhosis have a markedly increased risk of developing hepatocellular carcinoma
- Incidence in compensated cirrhosis is ~3%/year
- 25-30% in 10 y.

Tests to diagnose HCC

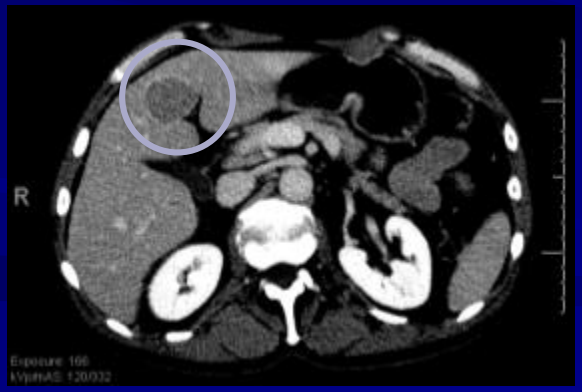
- Blood tests (AFP)
- Radiology (most important)
- Biopsy

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

HCC Surveillance

- Screening recommendations:
  - Radiology for HCC surveillance Q6 months for all cirrhosis patients

Other recommendations

Avoidance of Superimposed Insults

- Avoidance of:
  - Alcohol
  - Acetaminophen
  - Herbal medications

Vaccinations

All cirrhotic should be vaccinated to:

- Hepatitis A and B
- Pneumococcal vaccine
- Influenza vaccination

Liver Transplantation

- Liver transplantation is the definitive treatment for patients with decompensated cirrhosis
- Depends upon:
  - the severity of disease, absence of contraindications