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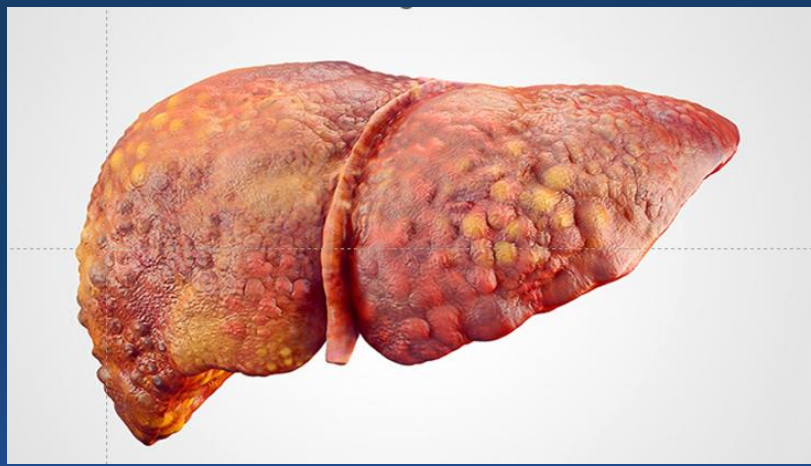
Liver Cirrhosis and its Complications

MED341



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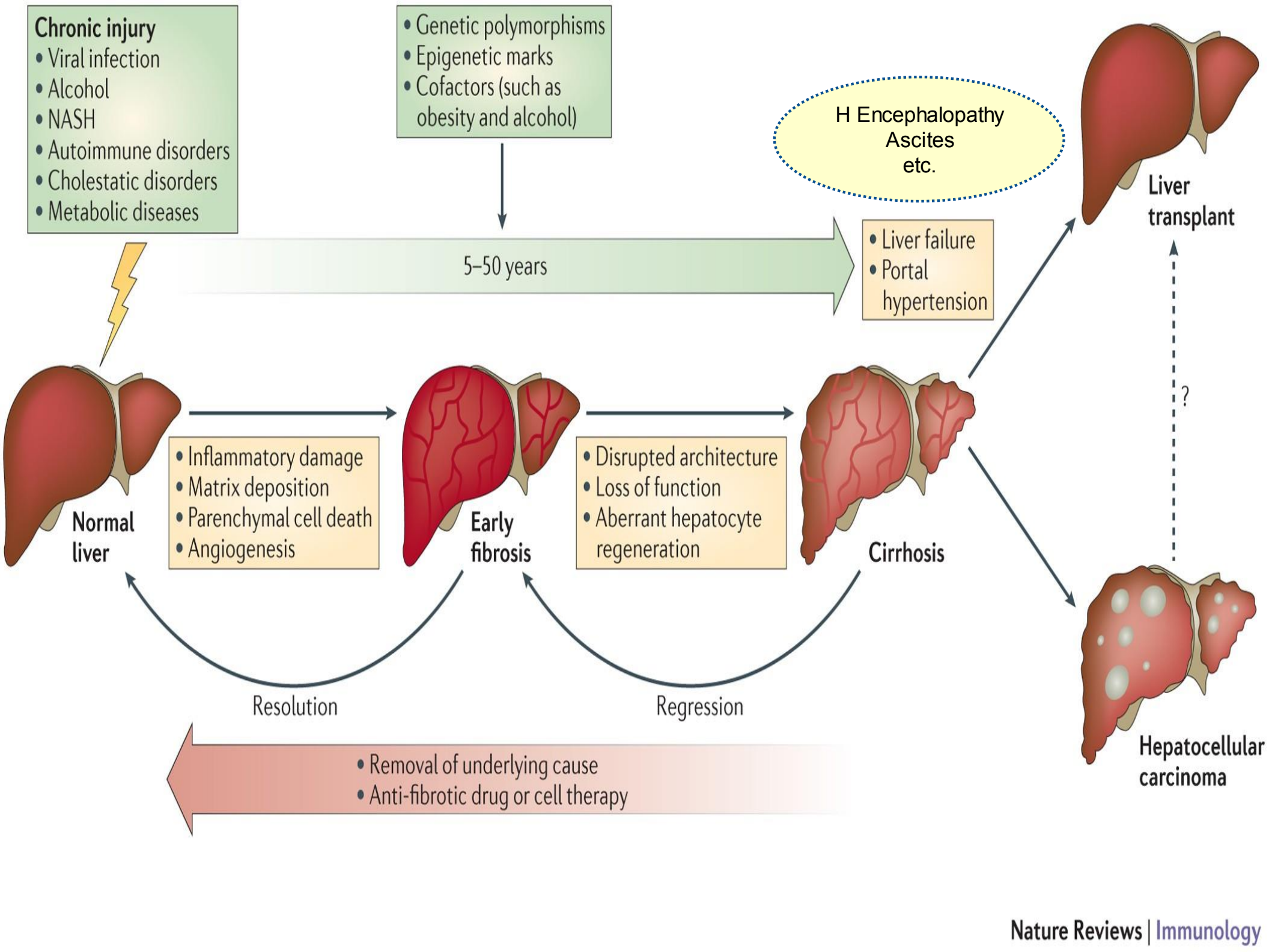
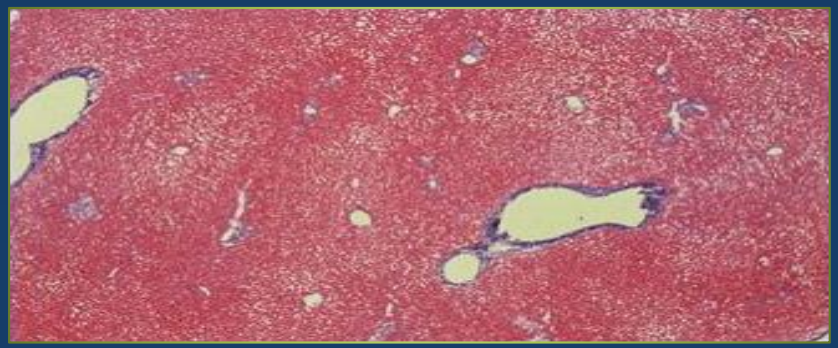
Objectives

- To know the cirrhosis definition, causes, and complications
- To correlate the pathophysiology of cirrhosis with its complications
- To acquire knowledge on how to approach patients with cirrhosis and its complications

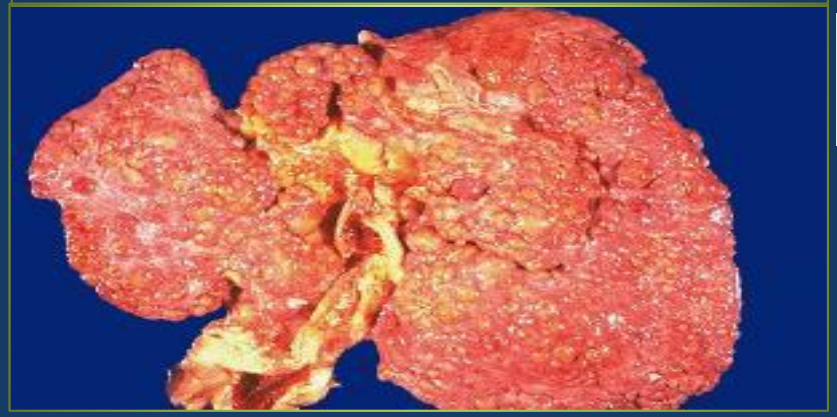


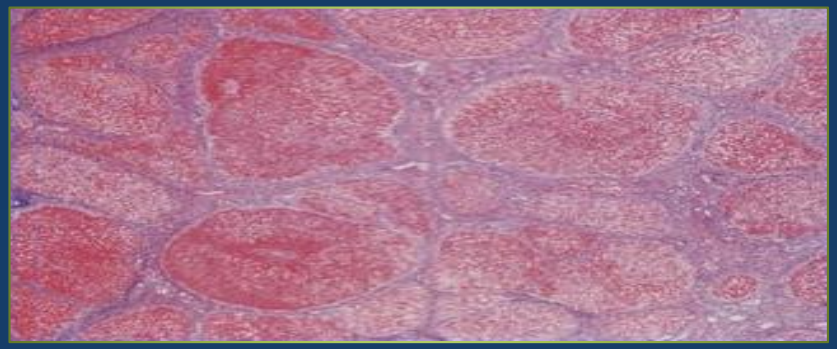
Nature Reviews | Immunology

NORMAL LIVER



CIRRHOTIC LIVER



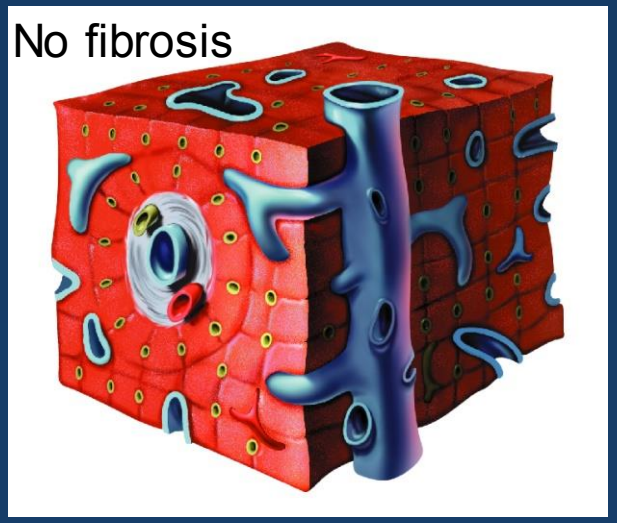


Cirrhosis: Late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules.

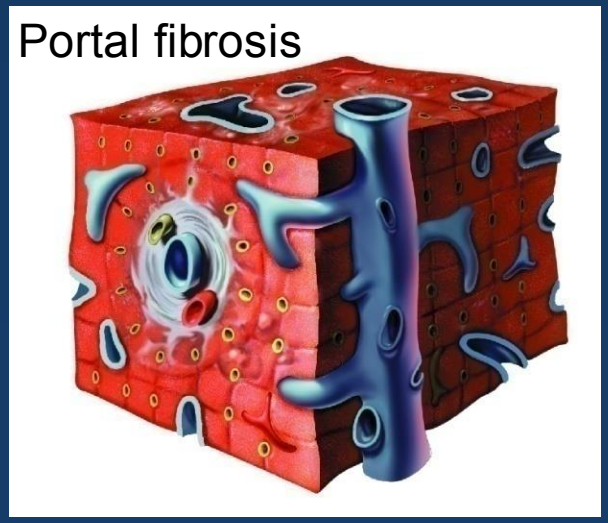
- The final stage of any chronic liver inflammation with fibrosis.
- Irreversible in its advanced stages, can be reversed in some if underlying cause is treated earlier.

Histologic Staging

Stage 0



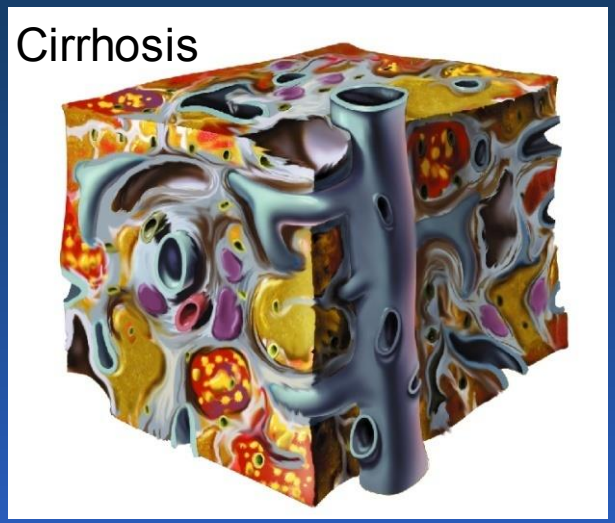
Stage 1



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 occurs when there is cirrhosis for a long time
-It is the beginning and requirement for most cirrhosis complications (significant portal hypertension)

Intrahepatic

Cirrhosis

1-Structural changes

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

2-Dynamic changes

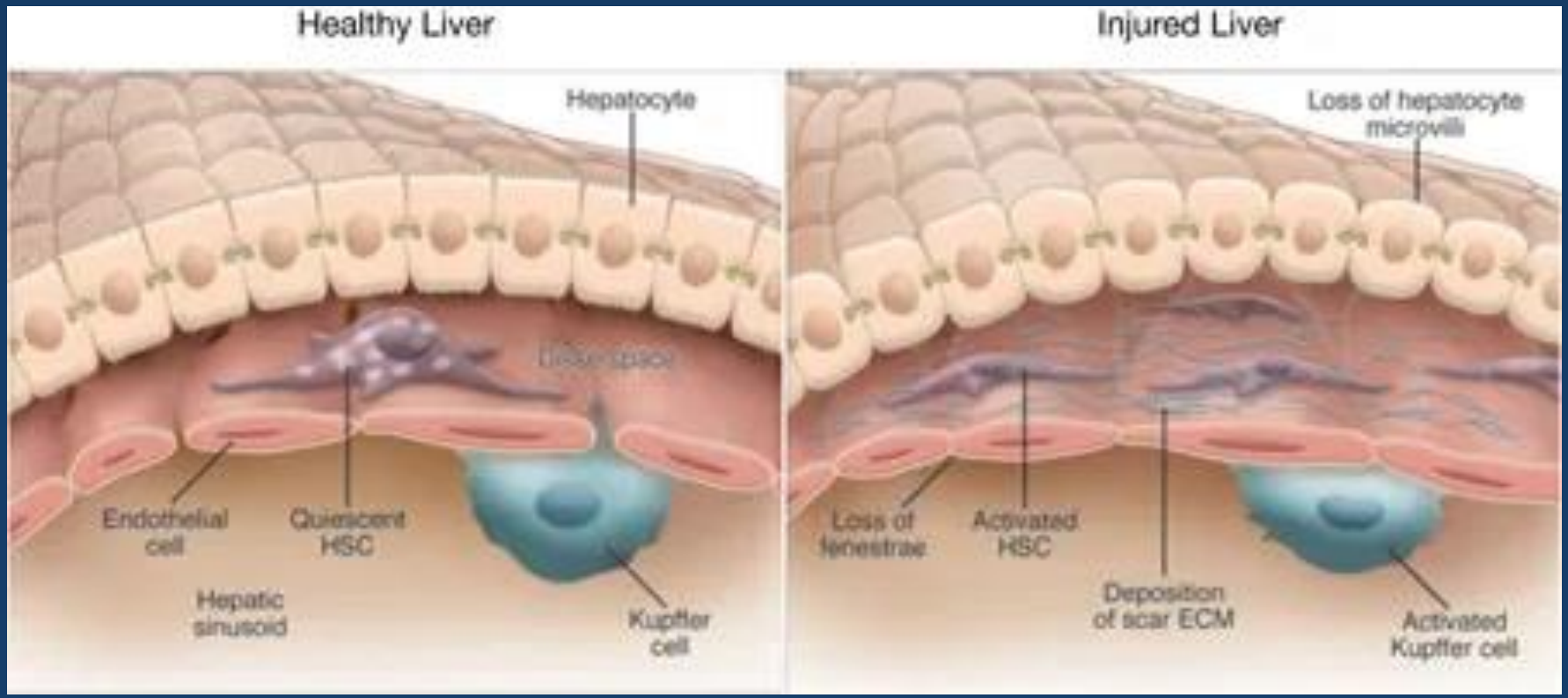
Intrahepatic cytokine-induced vasoconstriction and stellate cell contraction.

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

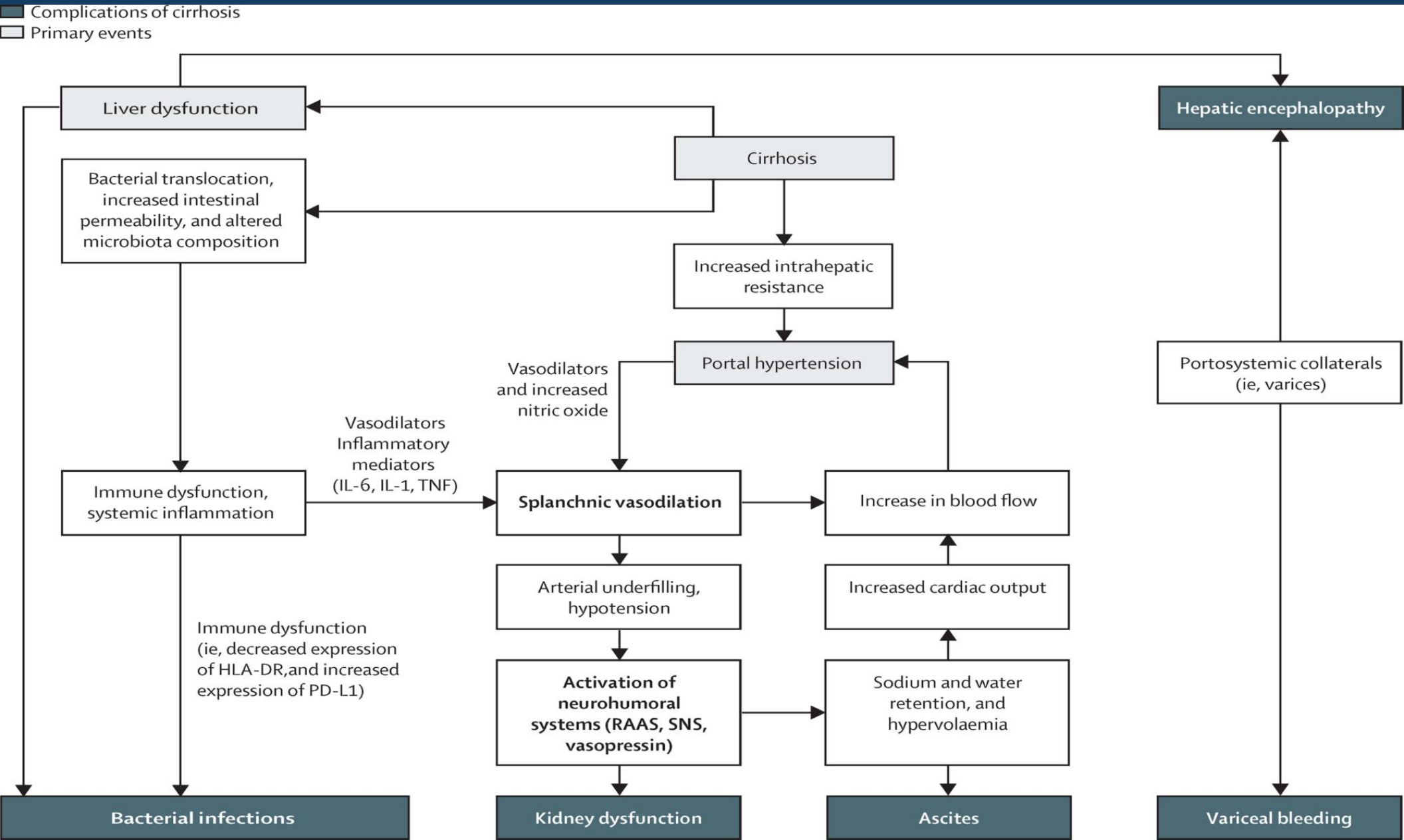


In healthy liver:
hepatic stellate cells are kept quiescent and their main function is to store vitamin A droplets

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



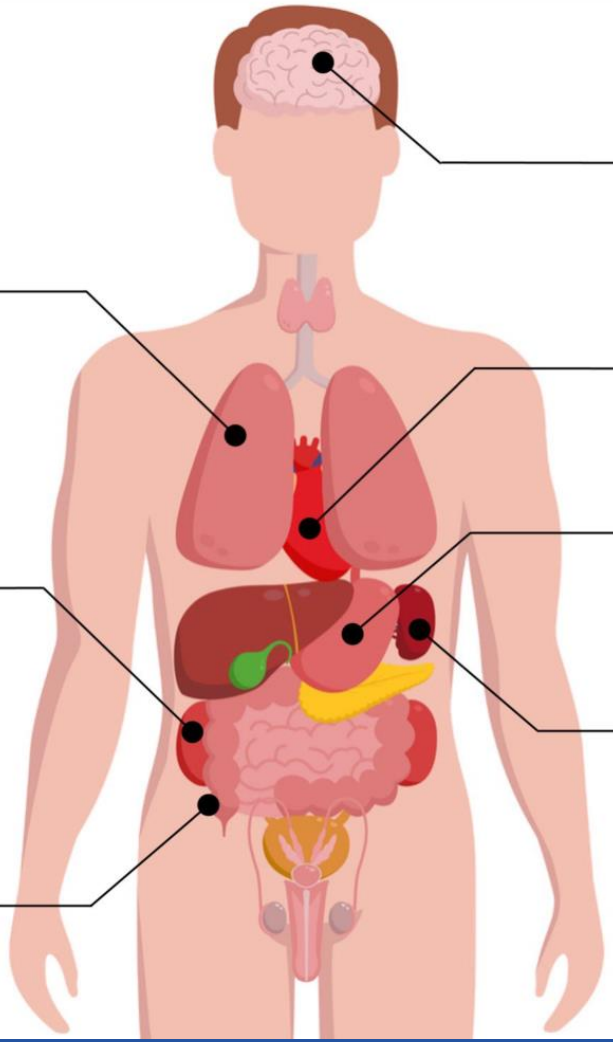
Common Cirrhosis Complications

- **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
- Others

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

COMPLICATIONS OF PORTAL HYPERTENSION



Hepatic Encephalopathy

Pulmonary

Hepatopulmonary syndrome
Portopulmonary hypertension
Hepatic hydrothorax

Cirrhotic Cardiomyopathy

Varices

Portal hypertensive gastropathy

Renal

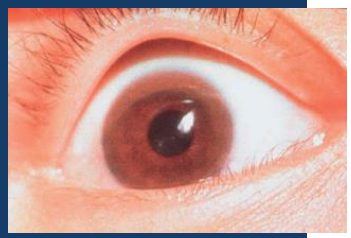
Hepatorenal syndrome

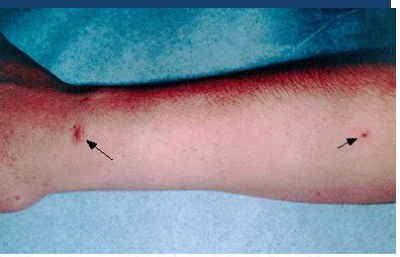
Splenomegaly

Hypersplenism
Pancytopenia

Ascites

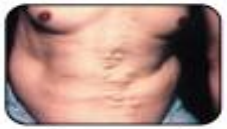
Spontaneous bacterial peritonitis



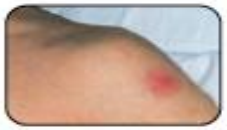


Spider angiomas This photograph shows two spider angiomas (spider telangiectasias) on the arm of a pregnant woman. A central feeding vessel, most easily seen in the lesion on the right, leads to other telangiectatic vessels, arranged in the shape of a spider, best appreciated in the lesion on the left.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

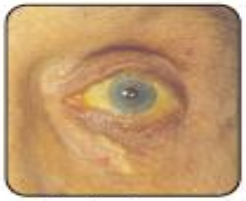


Gynaecomastia



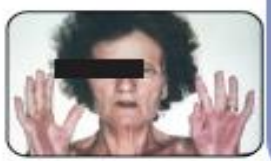
Spider naevi

2 Face
Jaundice
Spider naevi
Parotid swelling
Rhinophyma

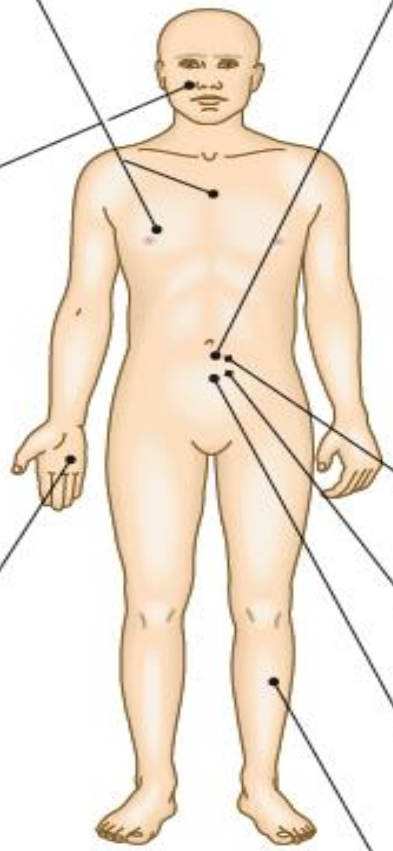


Xanthelasma and jaundiced sclera in a patient with chronic cholestasis

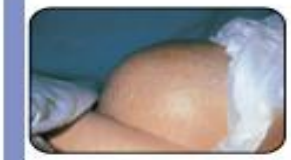
1 Hands
Clubbing
Dupuytren's contracture
Leuconychia
Smooth nails (from scratching)
Bruising
Flapping tremor (when arms outstretched and hands dorsiflexed)



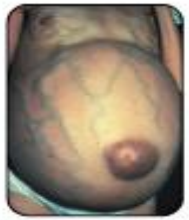
Palmar erythema



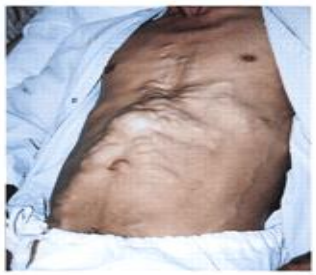
4 Abdomen: inspection
Scars
Distension
Movement
Veins
Testicular atrophy



Abdominal swelling in ascites



Dilated abdominal wall veins (caput medusae)



5 Abdomen: palpation
Hepatomegaly
Splenomegay

6 Abdomen: percussion
Ascites

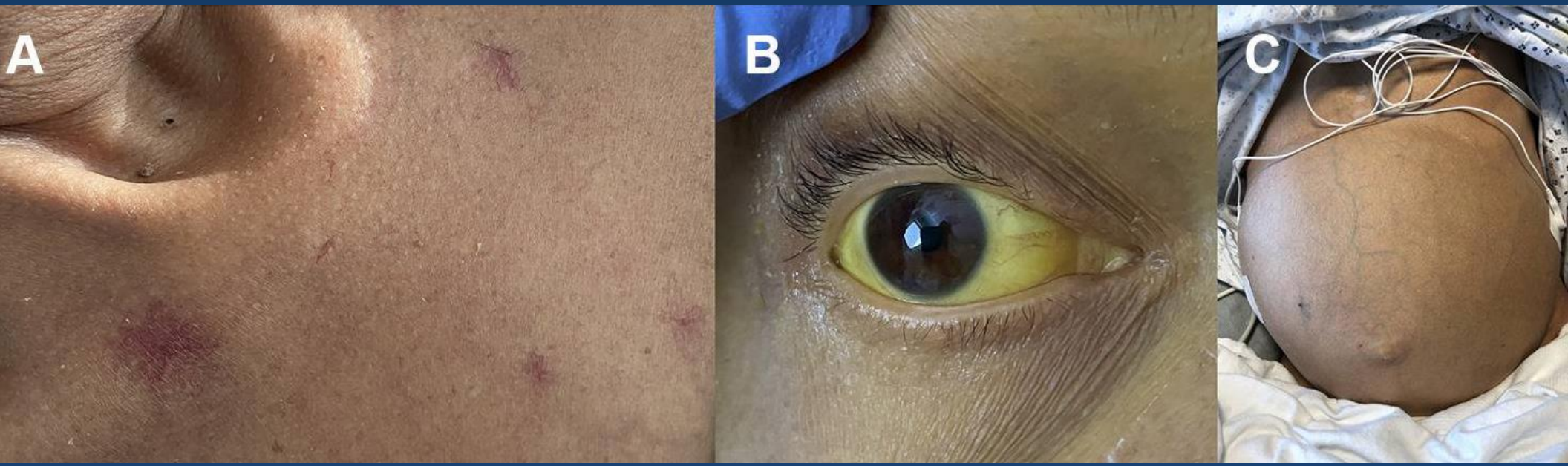
7 Abdomen: auscultation
Bowel sounds
Hepatic bruit

8 Legs
Bruising
Oedema

Observation

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

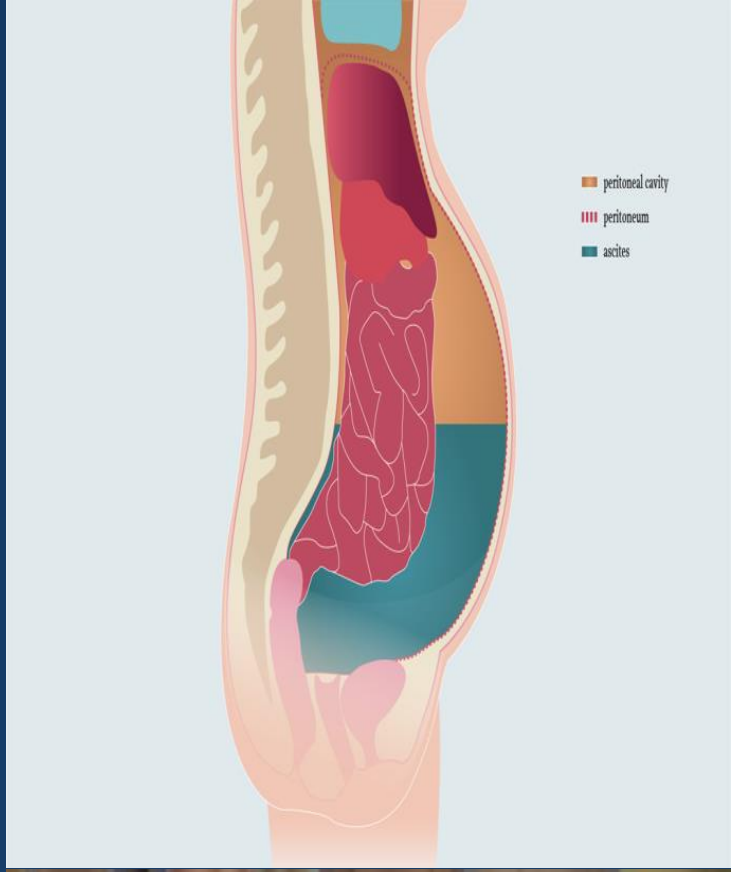
Clinical features of cirrhosis. (**A**) Spider nevi. (**B**) Severe scleral icterus. (**C**) Ascites.



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 Grades:

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

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

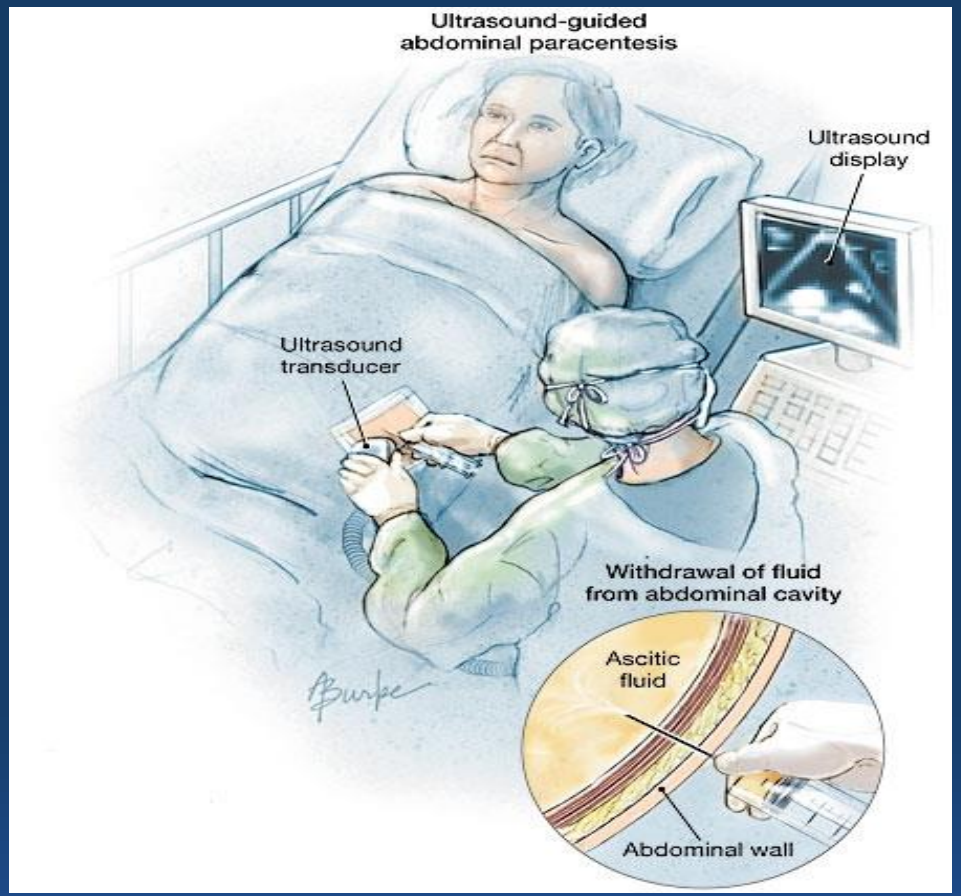
Grade 3 (severe) ascites, which manifests as tense abdominal distension with a fluid wave (Thrill).

Diagnostic paracentesis

Diagnostic paracentesis should be done for any clinically detectable ascites (grade 2 and 3):

1. Any new ascites should be tapped and analyzed!

2. All patients hospitalized for cirrhosis with ascites or other complications of cirrhosis (to rule out the presence of spontaneous bacterial peritonitis).



Ascitic fluid analysis

Ascites puncture

→ **Property observation**
Observe the color, turbidity, and odor of ascites.

Routine test

→ **Cell count and differential cell count** → **Neutrophils are 250/mm³ or more**

→ **Bacterial culture** → **Positive**

Culture should be performed before administration of antibiotics.
Put ascites in the culture bottle at the bedside.
Perform aerobic and anaerobic culture.

Neutrophils are 250/mm³ or more / **Positive** → **Spontaneous bacterial Peritonitis (SBP)**

Optional test ※1

→ **Measurement of concentration of total protein and albumin** → **Serum-ascites albumin gradient (SAAG)**

SAAG = serum albumin – ascites albumin

※1 If **carcinomatous peritonitis** is suspected, consider cytology and measurement LDH level of ascites. If **tuberculous peritonitis** is suspected, consider the mycobacterial smear stain, culture, PCR, and adenosine deaminase measurement. If **biliary peritonitis** is suspected, measure bilirubin level of ascites. If **pancreatitis** is suspected, measure amylase level of ascites. If **secondary bacterial peritonitis due to intestinal perforation** is suspected, consider gram staining, measurement of glucose, and LDH in ascites. If **chylous ascites** is suspected, measure triglyceride level of ascites.
(LDH: lactate dehydrogenase)

Differential diagnosis

SAAG is more than 1.1g/dL

- **Liver cirrhosis** (Chronic liver failure)
- Multiple liver tumor/liver metastasis
- Acute liver failure
- Alcoholic hepatitis
- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome
- Heart failure
- Hypothyroidism

SAAG is less than 1.1g/dL

- Nephrotic syndrome
- Carcinomatous peritonitis
- Tuberculous peritonitis
- Biliary peritonitis
- Pancreatitis

Yoshiji H, et al. Hepatol Res. 2021 Jul

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 the underlying cause
- Evaluation for liver transplantation (this is applied as well for any patients with cirrhosis complications)

Refractory Ascites

~10%

Defined as ascites that:

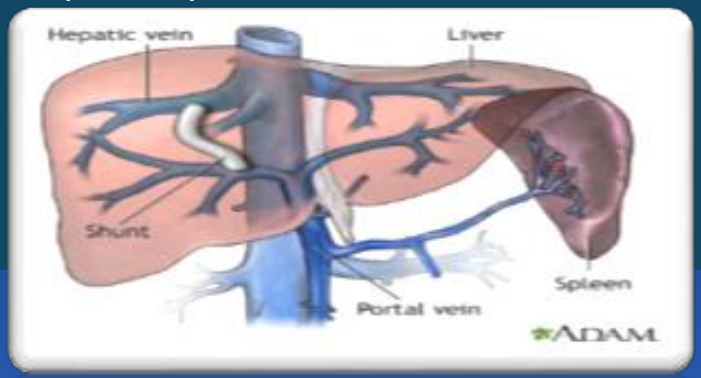
- Unresponsive to sodium-restricted diet and high dose diuretic treatment

Or

- Development of clinically significant complications of diuretics

Rx:

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



3. Refer to 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?

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

- What is the impact?:
  1. Associated with development of other cirrhosis complications, such as
     - H. encephalopathy
     - Variceal bleeding
     - Kidney injury
     - More liver dysfunction and failure. etc
  2. Frequent admissions
  3. Higher morbidity and mortality

Presentation of infection in cirrhosis

- Not always specific
- Sometimes:
  1. Signs of systemic inflammation (i.e. fever, high white blood cell count, high C-reactive protein, and tachycardia)
  2. 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

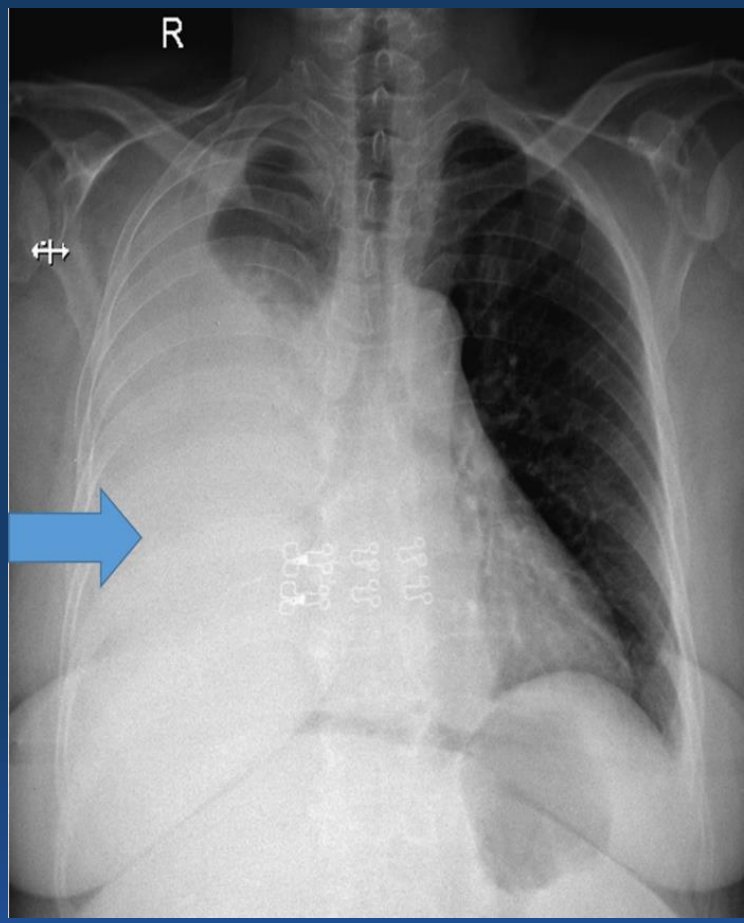
Hepatic Hydrothorax

- Pleural effusion in a patient with cirrhosis in the absence of cardiac, pulmonary, or pleural disease.

- 5-10% of cirrhosis patients.
- Commonly Rt side
- Cause: movement of ascitic fluid into the pleural space through defects in the diaphragm.

- Dx
  - High SAAG
  - Transudative fluid

- Management is similar to ascites.
- Thoracentesis may be required for diagnosis or therapeutic.



Acute kidney injury (AKI) in cirrhosis

- -Acute kidney injury (AKI) in up to 30–50% of hospitalised patients with decompensated cirrhosis
- Prerenal, hepatorenal syndrome, intrinsic, or postrenal AKI
- Prerenal AKI is the most frequent cause

Precipitating factors : (commonest)

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

Acute kidney injury-hepatorenal syndrome (HRS-AKI)

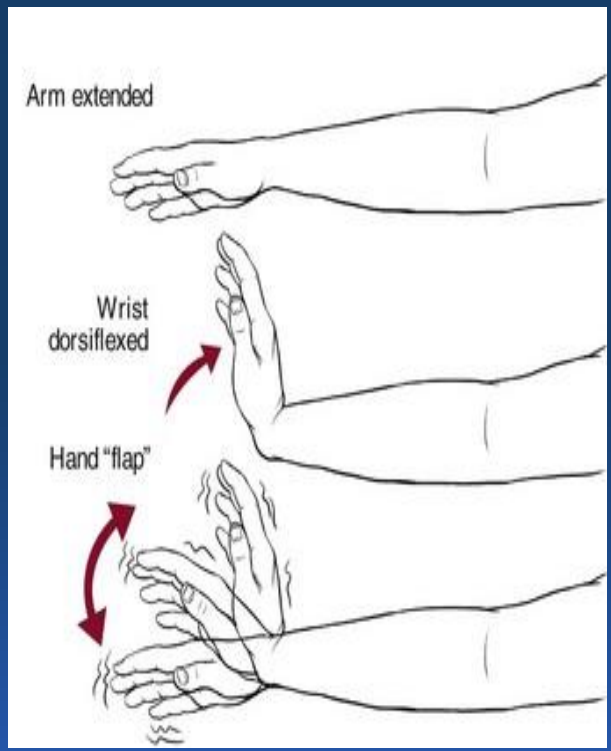
-Acute kidney injury–hepatorenal syndrome is a unique form of functional kidney failure that develops in patients with advanced cirrhosis, due to severe renal vasoconstriction.

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

Hepatic encephalopathy (HE)

- HE is a spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction and/or portosystemic shunting

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

Mechanims behind that: Not fully clear

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

Broadley 2 major pathophysiologic changes:

1. →activation of inhibitory neurotransmitter systems (gamma-aminobutyric acid, serotonin)
2. → 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**

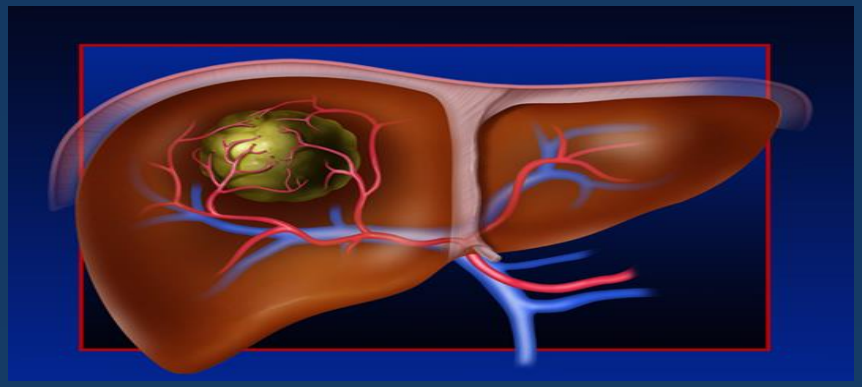
Rx

1. Identify and treat precipitating factors for HE

2. Measures to lower the blood ammonia concentration

   - Non-absorbable disaccharides (lactulose or lactitol)are the first choice for treatment, with aim of 3-4 bowel motions per day

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



Hepatocellular Carcinoma (HCC)

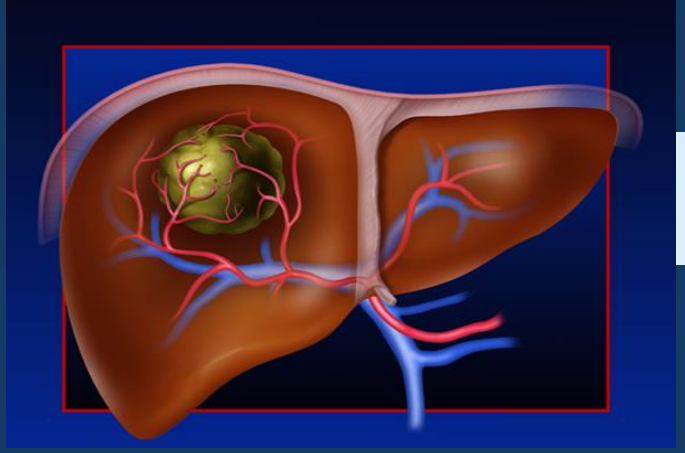
- Cirrhosis from any cause is a risk factor for HCC incidence (~3%/year) (25-30% in 10 y).

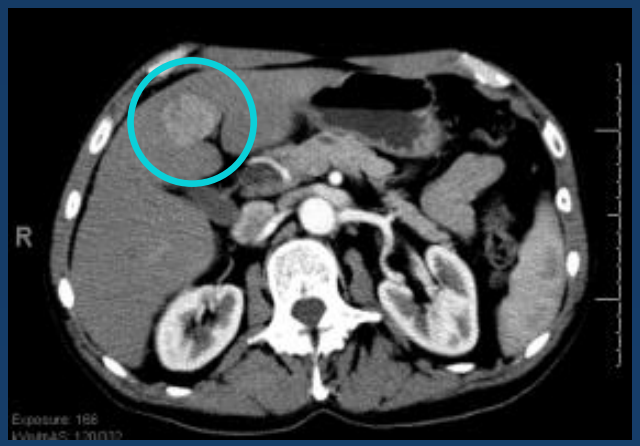
>>(So regular screening is recommended)

How to diagnose HCC?

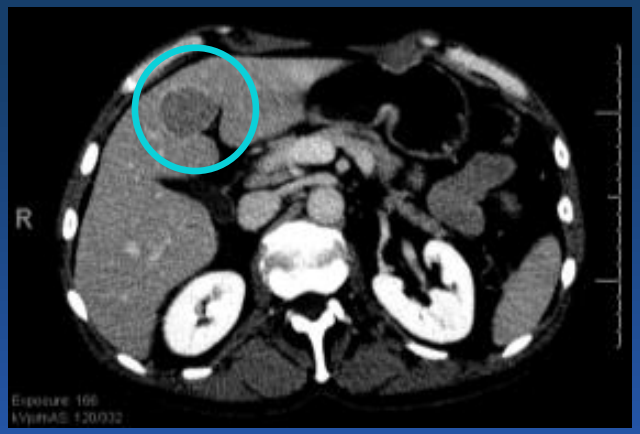
- Radiology (most important)
- Biopsy
- Blood tests: alphafetoprotein (AFP) high in some patients

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

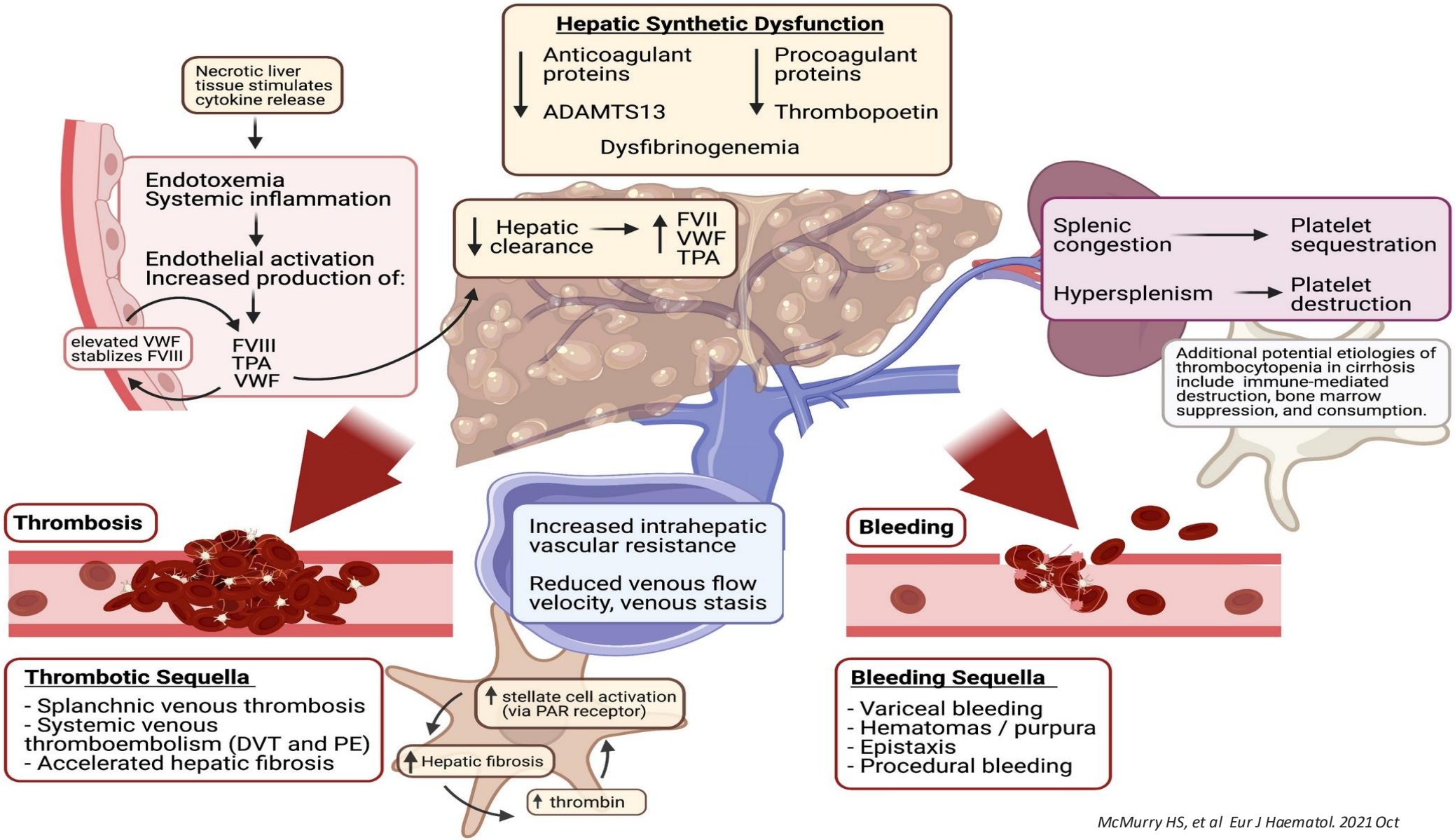
- Dynamic imaging (MRI, CT) follows tumor density with time after IV contrast bolus
  - Classical features: arterial enhancement and venous washout

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

The hemostatic and thrombotic complications of cirrhosis



McMurry HS, et al Eur J Haematol. 2021 Oct

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?

- Symptoms
- Signs
- Lab and imaging
- Management

Clinical manifestations

- **No symptoms (Most patients in compensated cirrhosis)**

Patients can be discovered incidentally to have cirrhosis for first time without clear symptoms

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- Symptoms of cirrhosis (sometimes non-specific symptoms, e.g. fatigue etc..)

- Symptoms of decompensations (such as ascites, HE, etc. 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

Laboratory
CBC (WBC, Hb, Platelets)
Normal in early diseases
Low platelets with portal hypertension
Hb may be low (? Chronic GI loss)
WBC (if high, usually indicate infection)
LFT (ALT, AST, ALP, Albumen, Bilirubin)
Could normal or mildly elevated in early cirrhosis.
Variable depends on the etiology
-Moderately elevated aminotransferases (often with an AST: ALT ratio >1, even within a low lab normal range)
Albumin*: low in advanced disease (check other causes of low albumin)
Bilirubin*: can be normal in early disease, high in advanced disease.
Coagulation profile
Prolonged prothrombin time/elevated INR*
Kidney and electrolytes
Hyponatremia
High Creatinine

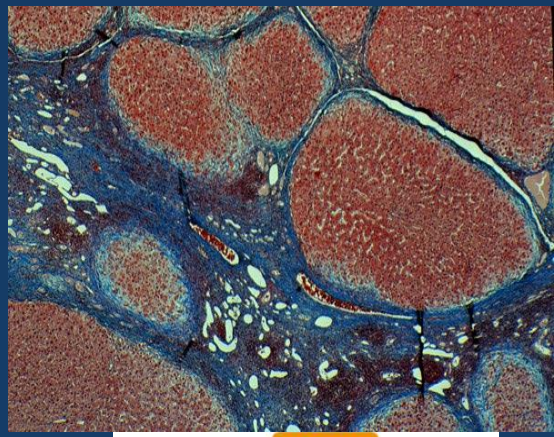
Radiology
Liver surface nodularity
Hypertrophy of the caudate or left lobes
Portosystemic collaterals*
Cirrhosis complications:
• Ascites*
• Hepatocellular carcinoma*
• Portal/splenic/superior mesenteric vein thrombosis*

* With advanced disease

Diagnostic tests for evaluation of the etiology of liver cirrhosis

Diagnostic test	Disease process
Hepatitis B surface antigen, positive viremia on highly sensitive hepatitis B virus DNA assay	Chronic hepatitis B
Anti-hepatitis C virus, hepatitis C virus RNA (confirmatory)	Hepatitis C
Antismooth muscle antibody, antinuclear antibody	Autoimmune hepatitis
Antiliver kidney microsomal antibody, antisoluble liver antigen antibody (both less common)	Autoimmune hepatitis
Iron level, serum ferritin, transferrin saturation	Hemochromatosis
Ceruloplasmin, 24 urine copper	Wilson disease
Alpha-1 antitrypsin phenotype	Alpha-1 antitrypsin deficiency
Lipid panel, hemoglobin A1c, hepatic ultrasonography	Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis
Aspartate aminotransferase > alanine aminotransferase, elevated gamma-glutamyl transferase, elevated mean corpuscular volume	Alcoholic liver disease
Antimitochondrial antibody	Primary biliary cholangitis

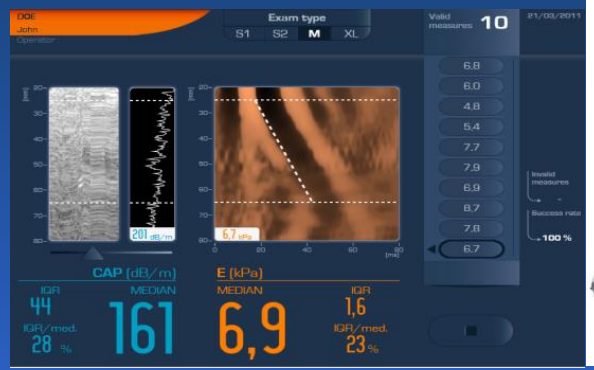
Diagnosis confirmation of compensated cirrhosis?



1. 1-Biopsy (histology)

2. 2-Noninvasive tests
   1. Serum score systems
   2. Elastography (e.g fiobroscan)

3. *Presence of liver decompensation manifestations with classical routine lab and images of cirrhosis are enough.*



How to assess 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%

Thank You

Best of Luck