Lecture 24

Editing file

Medicine Team

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Liver Cirrhosis & its Complications

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.

Color index:

Original text Females slides Males slides
Doctor's notes Text book Important Golden notes Extra

Liver Cirrhosis

Definition

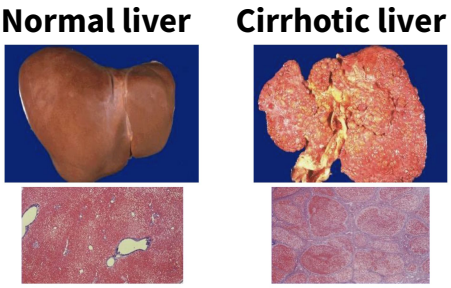
- **Cirrhosis:** Late stage of chronic liver inflammation and **fibrosis**, in which liver parenchyma is distorted and replaced by fibrous tissue and **regenerating nodules.**
- Cirrhosis is **final stage of any chronic liver inflammation**. It is **irreversible in its advanced stages**, can be reversed in some if underlying cause is treated.

◀ Types

The impairment of liver function in liver cirrhosis are either:

a. **Compensated liver Cirrhosis:** Asymptomatic, the liver is fibrosed but still maintain its function, Liver enzymes is either normal or elevated.

b. **or Decompensated liver Cirrhosis:** Symptomatic, The liver is extensively fibrosed for prolonged time that can't maintain its function and start to go for liver failure.



◀ Histologic Staging & Pathophysiology:

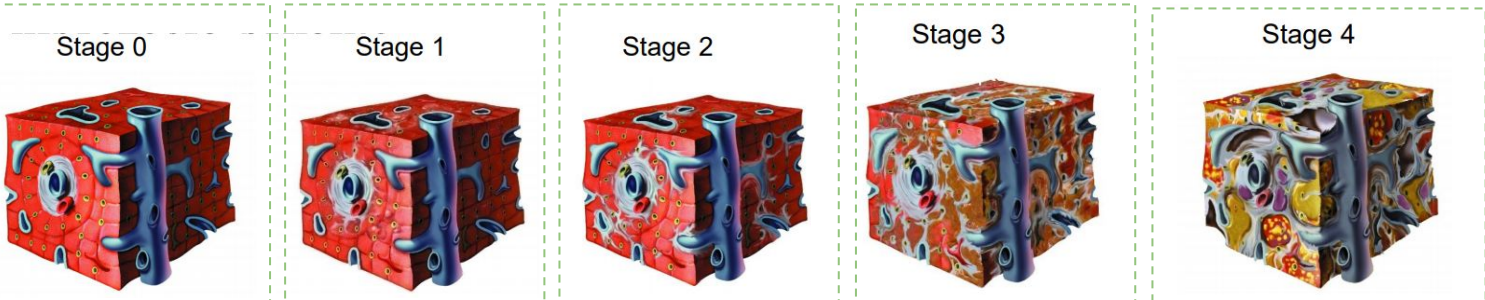
- Liver cirrhosis is diffuse disease affecting the whole liver.

Irreversible chronic injury of the hepatic parenchyma.

→ Extensive fibrosis replaces damaged or dead hepatocytes → distortion of the hepatic architecture.

→ Formation of regenerative nodules (if no nodules present no cirrhosis is there).

→ Portal hypertension (Nodules formation and architecture distortion → resistance to blood flow → Portal hypertension), Vascular[1] and humoral changes



No fibrosis

Chronic fibrosis start to appear around a portal tract

Crossing of fibrosis to nearby tissue.

Fibrosis start to reach other portal tracts (AKA: Bridging fibrosis).

Fibrosis will begin to reach to the lymph nodes and regenerative nodules formation.

1: The distortion of liver anatomy causes two major events, 1- Decreased blood flow through the liver. 2-Impairment of normal liver function.

Etiology

Mnemonic: VW HAPPENS

Viral hepatitis (HBV, HDV, HCV)[1]

The most common cause worldwide.

- It has to be **chronic Viral hepatitis** (hence why HAV & HEV are not considered)
- **HCV**
  - Associated with IV drug abusers.
  - Diagnostic Tests: PCR
  - Treatment: Sofosbuvir-velpatasvir (for all genotypes).
- **HBV**
  - usually associated with sexuall contact
  - Diagnostic Tests: +ve surface antigen for longer than 6 months, PCR
  - Treatment: Adefovir or Lamivudine or Interferon.
- Can be associated with polyarteritis nodosa.
- HDV is the most aggressive one.

Non-alcoholic Steatohepatitis (NASH)[1]

- Associated with inflammation and fibrosis of the liver and has the potential to progress to cirrhosis. NASH is potentially premalignant.
- Associated with Obesity, Diabetes, Hyperlipidemia, Corticosteroid use.
- There is an increasing incidents of NASH especially in Saudi Arabia.

Discussed in further details in a future lecture

Alcoholic Steatohepatitis (ASH)[1]

"Ethanol" **The most common cause in the western world.**

- Like all drugs causing liver disease gives a **greater elevation in AST compared to ALT**.
- Investigations: elevated MCV
  - May have xanthelasma because abnormality in lipid metabolism.

Autoimmune

1. **Primary Biliary Cirrhosis/Cholangitis (PBC).** B = بنت = usually shy = intra
   - progressive destruction of **intrahepatic bile ducts** causing cholestasis eventually leading to cirrhosis.
   - Affects **women** in 40s or 50s.
   - Presents with pruritis with or without jaundice. In advanced disease there is xanthelasma (due to secondary hypercholesterolemia).
   - The most accurate blood test is Antimitochondrial antibody (AMA).
2. **Primary Sclerosing Cholangitis (PSC).** S = son = bold = extra
   a. Progressive obliterating fibrosis of **intra and extrahepatic ducts** eventually leading to fibrosis.
   b. More common in **male** than female.
   c. 75% or more occurs in association with IBD.
   d. Diagnosis:
      i. MRCP
      ii. The most accurate test is Endoscopic retrograde cholangiopancreatography: shows irregularity of calibre of both intra- and extrahepatic ducts.
   e. Treatment: liver transplantation
3. **Autoimmune hepatitis (AIH).**
   - Circulating auto-antibodies (antinuclear, smooth muscle, soluble liver antigen, Liver/kidney microsomal antibodies) (ASMA) (ANA) "Hypergammaglobulinemia" .
   - May have xanthelasma because abnormality in lipid metabolism.
   - **On histopathology:** Rich plasma interface is a hallmark of AIH.

1: the commonest causes

Etiology *(cont.)*

Metabolic & Hereditary disorders

1. **Alpha 1 antitrypsin deficiency (A1AT).**
   - Combination of liver disease and emphysema in young patient (under 40) who is non smoker.
   - Presents with: **COPD & Cirrhosis.**
   - Treat by replacing the enzyme.
2. **Wilson's disease (W.D).**
   - Disorder of abnormally decreased copper excretion from the body because of a decrease in ceruloplasmin. Copper builds up in the liver, Kidney, Red blood cells and nervous system.
   - Presents with: **Neurological symptoms**, coombs negative hemolytic anemia and renal tubular acidosis.
   - Diagnosis: slit-lamp examination for Kayser-Fleischer rings, reduced ceruplasmin, increased urinary copper.
   - Treatment: Penicillamine to decrease Cu loud, but the only definitive treatment is transplant.
3. **Hemochromatosis.**
   - Genetic disorder leading to **over absorption of iron** in the duodenum.
   - Presents with : Fatigue and joint pain, Erectile dysfunction in men and Amenorrhea in women, Skin darkening, Diabetes, Restrictive cardiomyopathy.
   - Diagnosis: Increased serum iron, ferritin (>500ug/L or >240nmol/L), transferrin (>45%) and Decreased iron binding capacity.
   - Treatment: Phlebotomy (best), deferoxamine.

Vascular

Budd-Chiari syndrome:

- Definition: obstruction to the venous outflow of the liver owing to occlusion of the hepatic vein.
- Causes:
  - ⅓ of patients —> unknown
  - **hypercoagulability states** (e.g. paroxysmal nocturnal haemoglobinuria, polycythaemia vera) or thrombophilia, taking the contraceptive pill, or leukaemia.
  - Other causes: occlusion of the hepatic vein, renal or adrenal tumours, hepatocellular carcinoma, hepatic infections (e.g. hydatid cyst), congenital venous webs, radiotherapy or trauma to the liver.
- Heart failure
- portal vein thrombosis.
- Hypoxic damage and necrosis of hepatocyte.

Biliary

- **Sclerosing Cholangitis.**

Drugs

- Methotrexate, acetaminophen toxicity.

9.Others "something else" (polycystic disease, granulomatous disease etc..)

Approach to patients with cirrhosis

◀ History:

Presenting symptoms	• **Asymptomatic** mainly.
	• Nonspecific constitutional symptoms, such as fatigue, weakness, and weight loss, etc..
	• Symptoms of decompensation
	  ○ Abdominal distension (ascites and hepatomegaly).
	  ○ Coffee-ground vomitus and black stool (**melena**) secondary to GI hemorrhage.
	  ○ Altered mental status in hepatic Encephalopathy.
	  ○ Lower extremity swelling.
	  ○ Jaundice
	  ○ pruritus.
	• Hepatocellular carcinoma is the only complication that can happen even with compensated liver cirrhosis (Many patients come with HCC as the first presentation).
	• Other less common symptoms: respiratory (pulmonary hypertension, hepatic hydrothorax..)

Past and drug history	• History of liver disease (all chronic liver disease can lead to cirrhosis). • Surgery and dental. • Metabolic syndrome. • Drugs (Methotrexate, amiodarone, amoxicillin/clavulanate etc..).
Family history	• Wilson Disease. • Hemochromatosis. • Apha-antitrypsin deficiency. • Viral hepatitis.
Social history	• Risk-taking behaviors: IV drug use, sexual contact, and tattoos. • Alcohol (amount, type & duration). • Travel history.

◀ Clinical features

Hand and nails

- **Clubbing**.
- **Leukonychia**: Low Albumin
- **Palmar erythema:** high Estrogen due to impaired estrogen metabolism
- **Bruising**: Thrombocytopenia & decrease coagulative protein synthesis
- **Cholesterol deposits.**
- **Dupuytren contracture.**
- **Cyanosis**: in patients with hepatopulmonary syndrome.

Chest wall features

- **Gynecomastia** in men: due to accumulation of estrogen
- **Telangiectasia:** Abnormal visible dilatation of blood vessels
- **Spider naevi.**

Approach to patients with cirrhosis

Facial features

- **Muscle wasting.**
- **Telangiectasia**.
- **Bruising**.
- **Parotid gland swelling** (in alcoholics).
- **Jaundiced sclera.**
- **Xanthelasma**: yellowish deposit of cholesterol underneath the skin

Abdominal features

- **Collateral**
- **Bruising**
- **Hepatomegaly & Splenomegaly**
- **Abdominal distension**
- **Hepatic bruit.**
- **Loss of secondary Sexual hair**
- **Testicular atrophy** in men due to estrogen.

◀ Investigations:

01 Liver Function Tests:

ALT:

- **Moderately elevated** aminotransferases (often with an AST:ALT ratio >1)
- A very early sign of advanced cirrhosis is reversed AST:ALT ratio (no more hepatocytes to produce ALT which is normally more than AST).
- ALT more specific than AST as AST found in myocardium and skeletal muscle cell.

ALP:

- Elevated (2 to 3 times the upper limit of normal).

If associated with advanced disease:

- Prolonged prothrombin[1] time/elevated INR.
- And Low serum albumin[1].
- Hyperbilirubinemia[1]: Increase in unconjugated bilirubin & decrease in conjugated bilirubin
- Hyponatremia[1]
- Elevated serum creatinine: hepatorenal syndrome.

02 CBC:

- **Thrombocytopenia:** One of the earliest manifestation (due to hypersplenism).
- **Leukopenia/neutropenia**: also because of hypersplenism.
- **Anemia.**

03 Investigate the cause of cirrhosis

1: Increasing bilirubin, falling albumin (or an albumin concentration of < 30 g/L (3.0 g/dL)), marked hyponatraemia (< 120 mmol/L) not due to diuretic therapy, and a prolonged PT are all bad prognostic features

Approach to patients with cirrhosis

04 Radiological studies

Mild to moderate disease	Advanced disease
• Surface nodularity. • Hypertrophy of the caudate or the left lobes. • Increased echogenicity (ultrasound). • Atrophy of the right lobe.	• Ascites. Splenomegaly • Portosystemic collateral. • Hepatocellular carcinoma (HCC). • Portal, splenic, superior, mesenteric vein thrombosis

◀ Confirming the Diagnosis:

To confirm and support the clinical and radiologic manifestations if needed.

A. Invasive:

1- Biopsy (Histology)**:** most accurate test of all liver cirrhosis etiology except autoimmune causes.

B. Noninvasive tests :

1- Elastography (e.g fibroscan): Measure liver elasticity and gives a grade.

2- Serum score system (CPT and MELD)

◀ Assess Severity and Prognosis of Liver Disease:

Assessing the severity helps in prognosis & evaluate the need of liver transplant. Serum albumin and prothrombin time are the best indicators of liver function: the outlook is poor with an albumin level below 28 g/L. The prothrombin time is prolonged commensurate with the severity of the liver disease

1. **Child-Turcotte-Pugh score or Child Criteria (CPT score). Has 2 clinical and 3 laboratory parameters**
2. MELD score (model for end-stage liver disease): **Not important**
   - MELD = 3.8 x serum **bilirubin** (mg/dL) + 11.2 x **INR** + 9.6 x serum **creatinine** (mg/dL) + 6.4

Child–Pugh Classification to Assess Severity of Liver Disease

POINTS	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin µmol/L to mg/dL divide by 17	<2.0 mg/dL (<34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	>3 mg/dL (>51.3 µmol/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 ratio	<4	4 to 6	>6
	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Scoring:

- **Class A** (5 to 6 points), 100-85% 2-year survival.
  - (least severe liver disease)
- **Class B** (7 to 9 points), 80-60% 2-year survival.
  - (moderately severe liver disease)
- **Class C** (10 to 15 points), 45-35% 2-year survival.
  - (severe liver disease)

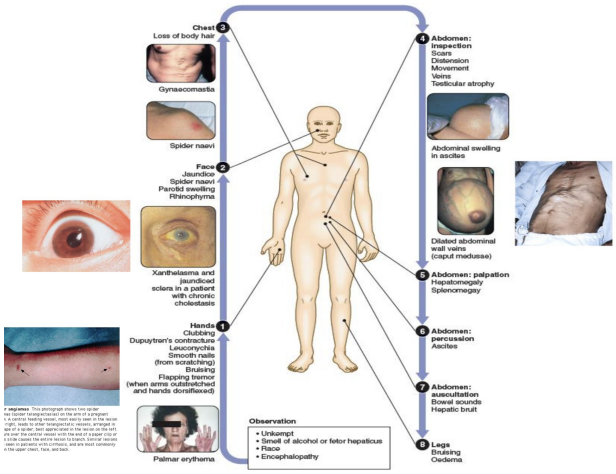
Cirrhosis Complications

◀ Common complications of cirrhosis:

Complications happens when liver fail to compensate (Decompensated Cirrhosis):

Decompensated Cirrhosis has 50% 2 years survival.

1. **Ascites**.
   - Asictes +/- refractory ascites.
   - Spontaneous Bacterial Peritonitis (SBP).
   - Hepatorenal syndrome.
2. **Hepatocellular carcinoma (HCC).**
3. **Hepatic Encephalopathy.**
4. Variceal hemorrhage. (separate lecture)
5. Pulmonary:
   - Hepatic hydrothorax.
   - Hepatopulmonary syndrome.
   - Portopulmonary HTN.



01 Portal hypertension

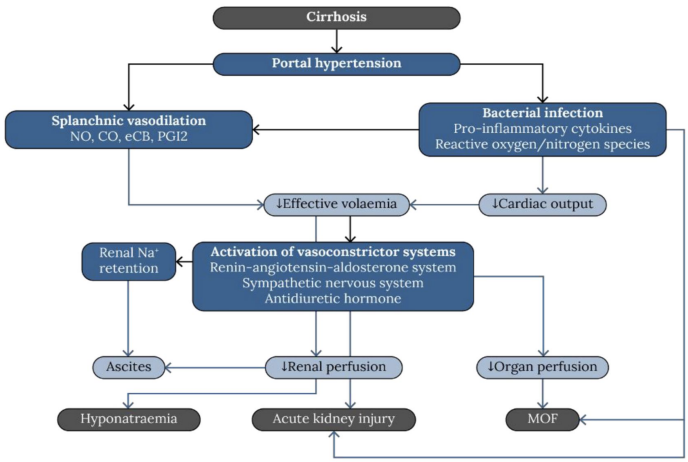
- **Developed as complication of cirrhosis. it is the beginning and requirement for most cirrhosis complications.**
- The normal hepatic venous pressure gradient (difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure) **is 5–6 mmHg**. Clinically significant portal hypertension is present when the gradient **exceeds 10 mmHg** and risk of variceal bleeding increases **beyond a gradient of 12 mmHg**.
- **Portal hypertension develop by Structural (mechanical) & Dynamic changes in the liver:**
  1. **Structural changes 70%:** Distortion of the liver microcirculation by:
     - fibrosis, nodules, angiogenesis, and vascular occlusion.
     - Can eventually affect the macrocirculation
  2. **Dynamic changes 30%:**
     - Hepatic stellate cells are activated into myofibroblasts → fibrogenesis and contractile potential (sinusoids, vascular smooth of the hepatic vasculature) **due to:**
       - Increased production of vasoconstrictors (eg, endothelins, angiotensin-II, norepinephrine, thromboxane A2)
       - Reduced release of endothelial vasodilators (eg, nitric oxide)

Figure explanation

Complication of cirrhosis is mainly caused by portal HTN

In cirrhosis with portal HTN there is:

- A splanchnic vasodilation and congestion of the gut.
- Bacteria and bacterial product translocation through the gut, which leads to subclinical endotoxemia. This will stimulate pro-inflammatory cytokines→ hemodynamic changes (decrease CO) and aggravation of the splanchnic vasodilation→ much more decrease in the effective blood volume.
- All of these result in decrease of effective blood volume → activation of RAAS, SNS & ADH (The vasoconstrictor systems) to increase effective intravascular volume → sodium retention and decreased renal perfusion → ascites, AKI and hyponatremia. If the vasoconstriction was very server in an advanced disease it could cause multi-organ failure due to low organ perfusion.



Cirrhosis Complications *(cont.)*

01 Portal hypertension *(cont.)*

◀ Causes

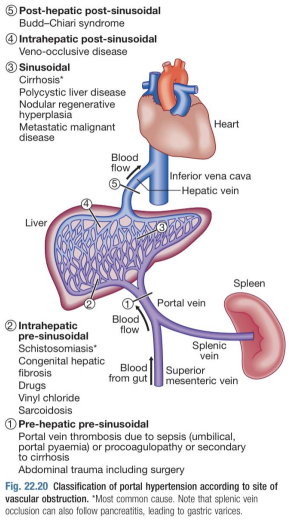


Fig. 22.20 Classification of portal hypertension according to site of vascular obstruction. *Most common cause. Note that splenic vein occlusion can also follow pancreatitis, leading to gastric varices.

Causes are classified in accordance with **the main sites of obstruction to blood flow in the portal venous system**.

- Extrahepatic portal vein obstruction: the usual source of portal hypertension in childhood and adolescence
- **cirrhosis: causes at least 90% of cases of portal hypertension** in adults in developed countries.
- **Schistosomiasis:** the most common cause of portal hypertension worldwide but is infrequent outside endemic areas, such as Egypt.

◀ Clinical features

The clinical features result principally from portal venous congestion and collateral vessel formation

1 Hypersplenism

- Splenomegaly is a cardinal finding and **a diagnosis of portal hypertension is unusual when splenomegaly cannot be detected** clinically or by ultrasonography.
- The spleen is **rarely enlarged more than 5 cm below the left costal margin** in adults.
- more marked splenomegaly can occur in **childhood** and adolescence.

2 Collateral vessels

- **caput medusae**
  - Cruveilhier–Baumgarten syndrome: a large umbilical collateral vessel has a blood flow sufficient to give a venous hum on auscultation
- **Esophageal varices**: can be a source of severe bleeding (variceal bleeding is the most important consequence of portal hypertension)
- **Rectal varices**: also cause bleeding, often mistaken for haemorrhoids

3 Fetor hepaticus

results from portosystemic shunting of blood, which allows mercaptans to pass directly to the lungs.

◀ Complications

01 **Variceal bleeding:** oesophageal, gastric, other (rare)

02 **Renal failure**

03 **Iron deficiency anaemia**

04 **Ascites & hypersplenism**

05 **Congestive gastropathy**

06 **Hepatic encephalopathy**

Cirrhosis Complications *(cont.)*

02 **Ascites**

Definition

A Pathologic accumulation of fluid in the peritoneal cavity. **It is the most common complication of liver cirrhosis.** It has a poor prognosis (unless Liver Transplant): Two-year survival of patients with ascites is approximately 50%.

◄ Causes (DDx):

- **85%** of **ascites** is due to **cirrhosis**, and 15% have other causes (eg, Nephrotic syndrome, malignancy, HF, TB).
- **Classification of ascites causes by the Serum Albumin-Ascites Gradient[1] (SAAG)**:

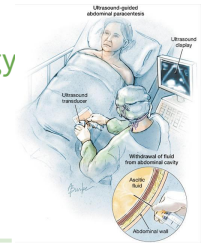
High albumin gradient (SAAG ≥ 1.1g\dL - 11 g/L) Transudate 90%	**Low albumin gradient (SAAG < 1.1g\dL - 11 g/L)** Exudate 10%
Portal HTN[2] (most common cause) related ascites. **Causes of portal HTN:** • Cirrhosis. • Heart failure Usually Right HF. • Constrictive pericarditis. • Alcoholic hepatitis. • Budd chiari. • Massive hepatic metastases.	**Non portal HTN ascites (peritoneal causes):** • Peritoneal carcinomatosis. • Secondary peritonitis. • Peritoneal tuberculosis. • Pancreatitis. • Serositis. • Nephrotic syndrome.

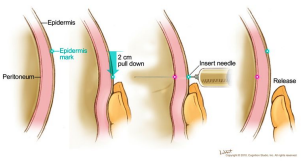
◄ Examination of ascites

- **Shifting dullness:** 83% sensitivity and 56% specificity in detecting ascites.
- **Flank dullness:** 1500 mL of fluid must be present before flank dullness is detected. More specific than shifting. If no flank dullness is present less likely ascites (< 10%).
- Respiratory distress accompanies tense ascites
- peripheral oedema

◄ Investigations

- **Any new ascites with or without pain, tenderness or fever should be tapped and analyzed**
- **First step in ascites management** to determine the etiology and role out infections.
- Routine test should be done in any case of ascites and other depending on the aetiology.





1: unlike ratios where we divide, in gradient we subtract.

2: 1st step in development of ascites is the presence of significant PHTN.

Cirrhosis Complications *(cont.)*

◀ Investigations *(cont.)*

Routine Tests	**1. Cell count and differential of the ascitic fluid** **2. Albumin** 3. **total protein: to measure Serum Albumin-Ascites Gradient (SAAG).**	**Optional: (when there is suspicion of infection)**	1. Gram stain and culture. 2. Glucose. 3. Lactate dehydrogenase. 4. Amylase: High in pancreatic ascites
Unusual Tests	1. Acid-Fast Bacilli smear (Not sensitive) and culture (50% sensitivity) better results from PCR and biopsy. 2. Cytology. 3. Triglyceride. 4. Bilirubin.	**Other Tests: Depends on the clinical scenario**	1. **Secondary peritonitis:** LDH, and glucose: Spontaneous bacterial peritonitis (SBP) from Secondary ascitic fluid CEA (Carcinoembryonic antigen) > 5 ng/mL OR ALP > 240. (gut perforation) **2. Cytology for peritoneal carcinomatosis** PH, lactate, Cholesterol, Fibronectin and Glycosaminoglycan are considered unhelpful test.

◀ Management:

- Depends on the cause, So the most important thing is to treat underlying cause.

The mainstay of management is combination of;
Dietary sodium restriction PLUS Diuretics (Spironolactone AND Furosemide)

With that being said, let's discuss the management in <u>further details</u>:

01 Initial treatment of ascites

1 Dietary salt restriction

- Limiting sodium intake to 88 meq or 2000 mg/day.

Note that: there is no need for fluid restriction except in patients with hyponatremia, or if they developed hyponatremia from the sodium restriction hear fluid restriction (Instead of the usual sodium restriction) is better for the patient.

1: unlike ratios where we divide, in gradient we subtract.

Cirrhosis Complications *(cont.)*

2 Diuretics

➔ (most successful regime is combination of **Spironolactone** and **Furosemide**).
- Monitor electrolytes and kidney function.

3 Other measures

- Discontinue NSAIDs: they Inhibit prostaglandin synthesis → potential renal vasoconstriction.
- Treat the underlying cause.
- Evaluation for liver transplantation any patient with complication needs to be assessed. because the most important thing is to treat underlying cause.

02 Treatment of refractory ascites (~10%)

Definition

Ascites that is:
- Unresponsive to sodium restricted diet & high dose diuretic treatment.
- Development of clinically significant complications of diuretics eg. Renal impairment, hyponatremia or hyperkalemia.

1. **Serial therapeutic paracentesis** (Ascites tap) (LVP) every 2 weeks
2. **Albumin** (if draining > 5L of fluid).
3. **Liver transplantation**[1]
4. **Transjugular intrahepatic portosystemic stent-shunt (TIPS)**[2,3]
5. **Peritoneo-venous shunt**[3]**.**

An area for your notes

1: Liver transplantation is the ultimate treatment for refractory ascites, however, not everyone is a candidate for it (Age/Comorbidities).
2: Through bypassing the liver by connecting the portal vein with the hepatic vein.
3: TIPS and petineo-venous shunt are an absolute contraindication in Hepatic encephalopathy. why? ammonia will be diverted to the systemic circulation directly (Without being detoxified in the liver) which will worsen Hepatic encephalopathy, it may even cause hepatic encephalopathy in normal patients.

Cirrhosis Complications *(cont.)*

◄ Complications of ascites:

01 Spontaneous bacterial peritonitis (SBP): (AKA: mono-microbial peritonitis)

- **Definition:** Development of a bacterial infection in the peritoneum, despite the absence of an obvious source for the infection.
- **Etiology:** Usually due to the translocation of gut bacteria and flora to the peritoneum leading to infection of ascitic fluid. (spontaneous means idiopathic no perforation)
- **Causes:**
  - Most cases of SBP are due to gut bacteria such as **E. coli** and **Klebsiella.**
  - Sometimes others: Streptococcal Staphylococcal or Enterococcus infections.
- **Diagnosis:**
  - **PMN count** (>250 cells/mm3)[1]
  - **Positive ascitic fluid bacterial culture.**
- **Clinical manifestations:** all, some, sometimes-none of the symptoms
  - Fever, Abdominal pain/tenderness
  - Altered mental status

  They mostly present with "None" of the symptoms above. usually present with worsening of their complication or only hepatic encephalopathy. Here you must suspect SBP.
- **Treatment:**
  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 which occur in 30-40% of SBP (major cause of death).

02 Secondary bacterial peritonitis (AKA: poly-microbial peritonitis)

- Caused by an obvious cause eg: Perforation and has high WBCs count.
- Diagnosis: If Secondary bacterial peritonitis is suspected do CT scan.

03 Hepatic hydrothorax

- **Definition:** Pleural effusion (Commonly right side.) in a patient with cirrhosis and **no evidence of underlying cardiopulmonary** disease.
- **Prevalence:** 5-10% of cirrhosis patients.
- **Cause:** movement of ascitic fluid into the pleural space through defects in the diaphragm.
- **Diagnosis:**
  - Reveals a **transudative fluid**
  - Serum to fluid albumin gradient greater than 1.1.
- **Management:** similar to ascites: Na restriction & diuretics

1: normally its ~ 150 cells/mm3

Cirrhosis Complications *(cont.)*

04 Hepatorenal syndrome

- **Definition:** Development of **Acute Renal Failure** (Functional[1]). It **require presence of cirrhosis and ascites.**
- Marked peripheral vasodilatation leads to fall in systemic vascular resistance and effective hypovolemia. This in turn results in vasoconstriction of the renal circulation with markedly reduced renal perfusion. It has a poor prognosis.
- **Types:**
  - **Type I: rapid, aggressive.**
    - Acute renal failure due to cirrhosis progress in days. They die without liver transplant.
  - **Type II : slow, less aggressive.**
    - Present as: azotemia, oliguria, hyponatremia, hypotension,low urine sodium < 10 mEq/L.
- **Diagnosis:** by exclusion (Exclude dehydration, infection, drugs, and obstruction). The commonest cause of renal failure in cirrhotic patient is prerenal not Hepatorenal Syndrome.
- **Treatment:**
  - Correct underlying cause (liver cirrhosis) Reversed with **liver transplant (best option)**
  - Diuretic therapy should be stopped
  - **Albumin**: to correct intravascular hypovolemia
  - **Vasoconstrictors of splanchnic vessels**[2]
    - Terlipressin: with intravenous albumin, improves renal function in ⅓ of patients.
    - octreotide
    - midodrine
    - epinephrine
  - **Hemodialysis** (HD).

05 Hepatopulmonary syndrome

- **Definition:** hypoxaemia occurring in patients with advanced liver disease. It is due to intrapulmonary vascular dilatation with no evidence of primary pulmonary disease.
- **Clinical features:** triad of:
  - **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 with/out HPS (ascites).
- In severe disease patients have orthodeoxia (breathless on standing).
- **Diagnosis:**
  - **Transthoracic ECHO:** shows intrapulmonary shunting
  - arterial blood gases: confirm the arterial oxygen desaturation.
- **Treatment:** liver transplantation.

1. It's called "Functional" cause the parenchyma is normal but with a very severe vasoconstriction.
2: to oppose the vasodilation

Cirrhosis Complications *(cont.)*

05 Porto-Pulmonary HTN

- **Definition:** the presence of **pulmonary hypertension** in the **coexistent portal hypertension**. must be distinguished from the hepatopulmonary syndrome as in this group there is **pulmonary hypertension.**
- **Prevalence:** in cirrhotic patients is approximately 1-2%. (rare, but have high mortality rates)
- **Diagnosis:**
  - Suggested by echocardiography.
  - **Confirmed by right heart catheterization.**
- **Treatment:**
  - may respond to medical therapy.
  - Severe pulmonary hypertension is a **contraindication for liver transplantation**.

06 Hepatic encephalopathy

- **Definition:** Hepatic encephalopathy is a reversible brain dysfunction caused by liver insufficiency and/or portosystemic shunts.
- Occurs with advanced hepatocellular disease either chronic (Cirrhosis) or acute (Fulminant) it is also present in patient following surgical or TIPS shunts.
- **Manifestations:** wide spectrum of neurological or psychiatric:
  - abnormalities ranging from subclinical alterations to coma. Includes changes in:
    - intellect
    - emotions
    - personality
    - consciousness

Hepatic encephalopathy can be graded from 1-4

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

- **Causes:** precipitating factors include anything that increase ammonia production, absorption or entry into the brain

1. **Drugs** Benzodiazepine, narcotics alcohol.
2. **Hypokalemia**
3. **Portosystemic shunting** Radiographic, surgically placed or spontaneous shunts
4. **Infection**
5. **Hepatocellular carcinoma**
6. **Constipation**
7. **↑Protein load** including gastrointestinal bleeding, metabolic alkalosis
8. **Dehydration** Vomiting, Diarrhea, Hemorrhage, Diuretics or Large volume paracentesis.
9. **Vascular occlusion:** Hepatic or portal vein thrombosis.

Cirrhosis Complications *(cont.)*

06 Hepatic encephalopathy *(cont.)*

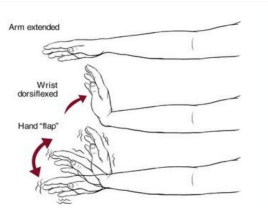
- **Pathophysiology:**

Different mechanisms: (it caused by multiple factor happening at the same time)

1. **Neurotoxin** (ammonia) liver convert ammonia to urea in urea cycle . if the liver is abnormal ammonia accumulation and affects brain.
2. Disruption of Blood-to-brain transport of neurotransmitter.
   - Activation of inhibitory (gamma-aminobutyric acid, serotonin) neurotransmitter systems.
   - Impairment of excitatory (glutamate, catecholamines) neurotransmitter systems.
   - Leading to enhanced neural inhibition.
3. Sepsis, neuroinflammation, and alterations in gut flora appear to be additional factors.

- Liver can't compensate for proteins intake, so there will be production of ammonia from these proteins by the action of gut microbiota. This ammonia will go to the blood → BBB → step 3,4.

- **Clinical features:**
  - Flapping tremor is a specific clinical finding in advanced liver disease.



- **Management:**

The aims of management is to:

1. **Identify and treat any precipitating factors that lead to HE**
2. **And to minimize absorption of ammonia:**

Lactulose First line of treatment

inhibit the conversion of NH4 to NH3.
(15–30 mL 3 times daily), increased gradually until the bowels are moving twice daily

01

02

nonabsorbable oral antibiotic (Rifaximin)

(400 mg 3 times daily) is a well-tolerated, non-absorbed antibiotic that acts by reducing the bacterial content of the bowel and has been shown to be effective.

LOLA

L-ornithine-L-aspartate → stimulates the metabolism of ammonia

03

04

Oral BCAAs

branched-chain amino acids (BCAA)

Cirrhosis Complications *(cont.)*

07 Hepatocellular carcinoma

- Patients with chronic liver disease or cirrhosis have a markedly increased risk of developing hepatocellular carcinoma.
- **Incidence** in **compensated** cirrhosis is ~3%/year and 25-30% in 10 y.
- **Risk factors:**
  - The main risk factor is **cirrhosis** (need u/s every 6 months for early detection)
  - Other aetiological factors include **aflatoxin** (toxin produced by Aspergillus which found in food contaminated with aflatoxin like Nut,milk and cheese), **Androgenic steroids, contraceptive pills** and **vinyl chloride** (found in plastic).
- **Prognosis:** Poor (median survival is only 6-20 months)
- **Investigations:**

Blood tests

- **(Alpha Fetoprotein AFP):** positive in only 50% of the patients.

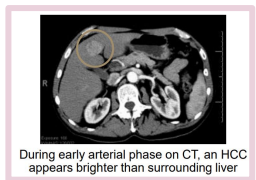
Biopsy

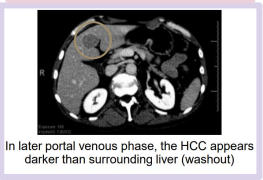
not used routinely for HCC only performed when there is diagnostic doubt as there is risk of tumor seeding in the percutaneous needle biopsy tract.

Radiological studies (Most Imp)

Dynamic CT and MRI

- Dynamic CT and MRI follows tumor density with time after IV bolus contrast.
- **high sensitivity and specificity**.
- Unlike most other tumors that require biopsy, **radiological testing in HCC is enough even for surgery and transplant.**
- In triphasic CT scan it will show Characteristic **Enhancement**, i.e. hyperdensity (light up) on the **arterial phase** followed by **washout** on the **portal/venous phase** (because it is not supplied by the portal vein).
- Dynamic CT and MRI follow several phases unenhanced phase, arterial enhancement phase, portal phase and delayed please, we take three CT images of the liver.
  - **Without contrast.**
  - Post IV injection: (**Enhanced arterial phase**) 20s following contrast injection.
  - **Delayed portal venous phase.** (washed out phase) 50s after the enhanced arterial phase .
  - Sometimes patients may have contrast retention for some reason in the first 50s, for them we do CT imaging after 5Min of the enhanced arterial phase (instead of the usual 50s). We call this **Delayed phase.**


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)

→ How to differentiate between HCC and normal liver parenchyma?

For diagnosis of HCC: both arterial enhancement and washout (portal/delayed) phases should be observed:

- → **HCC** are Hypervascular: the **tumor blood supply is 100% from the Hepatic artery (arterial supply → supply is seen during the arterial phase of the contrast CT)**
- → **liver parenchymal** (normally) has blood supply = 30% from hepatic artery and **70% from the portal vein (mostly venous supply → supply is seen mostly during the venous phase of the contrast CT).**

Cirrhosis Complications *(cont.)*

07 Hepatocellular carcinoma *(cont.)*

- **Treatment:**

Depends on several factors, including:

- The stage of the tumor
- stage of liver disease.
- Different scoring systems.

Treatment option are:

1. Liver Transplantation: the only option in late stages
2. Surgical resection: considered only in early stages
3. Ablation:
    a. radiofrequency (RFA)
    b. alcohol injection
4. Embolization:
    a. TACE; trans-arterial chemoembolization
    b. TARE: transarterial radio-embolization
5. Chemotherapy
6. Palliative

Management of Liver Cirrhosis

➔ Once a patient develops complications of cirrhosis, they are considered to have **Decompensated Cirrhosis**, with the exception of HCC that could happen even in compensated liver cirrhosis.

Cirrhosis is **irreversible** and frequently progress. options that may halt the progression of liver disease:

- managing complications seen in decompensated cirrhosis.
- Correcting the underlying cause
- venesection for haemochromatosis
- abstinence from alcohol for alcoholic cirrhosis

◀ 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.
- High survival rates after transplant, more than 90%.
- Source of liver: donor (living related) or deceased.

◀ General Recommendations for all cirrhotic patients :

Screening

- Radiology for HCC surveillance Q6 months for all cirrhosis patients with **ultrasound.**
- Endoscopy for varices.

Avoid insults

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

Vaccinations

All cirrhotic should be vaccinated to:

- Hepatitis A and B.
- Pneumococcal vaccine.
- Influenza vaccination.

Summary

Liver cirrhosis	
Definition	Late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules.
Progression	Chronic liver injury or Chronic hepatitis ⟶ Compensated Cirrhosis ⟶ Decompensated Cirrhosis ⟶ Death or liver transplantation.
Most common Aetiology	1. Viral hepatitis (HBV & HCV). 2. Alcoholic Steatohepatitis. 3. Non-alcoholic Steatohepatitis.
Investigations	**1. Lab tests:** LFT, CBC ,PPT, INR, Hyperbilirubinemia and Serum albumin **2. Radiology**
Confirm the Diagnosis	**Invasive:** Biopsy **Noninvasive tests:** Elastography & Serum score systems
Severity of Liver Disease	**1. Child-Turcotte-Pugh score.** **2. MELD score.**

Complications of liver cirrhosis		
1. Ascites: Accumulation of fluid in the peritoneal cavity		
Investigation	**Routine:** 1. Cell count and differential 2. Albumin and total protein To measure SAAG.	
Management	1. Dietary salt restriction. 2. Diuretics (Spironolactone & Furosemide combination).	
Refractory ascites	1. Unresponsive to sodium restricted diet and high dose diuretic treatment. 2. Development of clinically significant complications of diuretics.	
SAAG	**High albumin gradient (SAAG>=1.1g\dL)**: ● **Cirrhosis** / Alcoholic hepatitis. ● Heart failure / Constrictive pericarditis.	**Low albumin gradient (SAAG<1.1g\dL):** ● Peritoneal carcinomatosis ● Lymphoma. ● Nephrotic syndrome
Complications	**Spontaneous bacterial peritonitis:** Infection of ascitic fluid. **Diagnosis:** Ascitic fluid cell count⟶ PMN count (>250 cells/mm3) & a positive ascitic fluid culture **Treatment:** Cefotaxime + Albumin	

Complications of liver cirrhosis

2. Hepatic encephalopathy: is a reversible brain dysfunction caused by liver insufficiency and portosystemic shunts.

Pathophysiology	Neurotoxin (ammonia) → Cross BBB → Activation of inhibitory neurotransmitter systems→ Impairment of excitatory neurotransmitter systems → Enhanced neural inhibition.
Clinical Features	(Flapping tremor).
Precipitants	• Drugs. • Increased ammonia. • Dehydration. • Portosystemic shunts. • Vascular occlusion. • HCC.
Treatment	1. Lactulose (decrease absorption of ammonia. 2. Rifaximin or metronidazole (decrease GI bacteria that produce ammonia).

Complications of liver cirrhosis

3. Hepatocellular carcinoma (Hepatoma) HCC

Investigation	• **Blood tests:** (Alpha Fetoprotein AFP). • **Radiology:** Dynamic CT and MRI (See tumor density with time after IV bolus contrast. Requires both arterial enhancement and washout) • **Biopsy.**

Other Complications of liver cirrhosis

4.Hepatorenal syndrome:

- **Development of functional acute kidney injury in a patient who usually has advanced liver disease either cirrhosis or alcoholic hepatitis.**

5.Portopulmonary Syndrome:

- **The presence of pulmonary hypertension in the coexistent portal hypertension**

6.Hepatic Hydrothorax:

- **Pleural effusion in a patient with cirrhosis and no evidence of cardiopulmonary disease.**

7.Hepatopulmonary syndrome (HPS):

Triad of:

Liver disease , Increased alveolar-arterial gradient , Evidence for intrapulmonary vascular abnormalities

Lecture Quiz

Q1: A 58-year-old man with cirrhosis and ascites caused by chronic hepatitis C is hospitalized because of subtle personality change that progresses to drowsiness and confusion. The patient's wife reports that his stools have been darker than usual and that he has been unsteady upon arising the past few days. She also reports that he has been reluctant to take several of his medications recently as he has been reading about natural remedies. On physical examination, the patient is lethargic, disoriented, and uncooperative. He is afebrile, has clear lungs, normal heart, distended abdomen with shifting dullness, and no meningeal or focal neurologic findings. There is mild hyperreflexia and a nonrhythmic flapping tremor of the wrists. Stool is positive for occult blood. CT scan of the head is normal. What is the best initial therapy to address this patient's mental status changes?

A- Quetiapine 25 mg orally tid
B- Lorazepam 1 mg orally tid
C- Haloperidol 2 mg intramuscularly q 4 hours prn agitation
D- Lactulose 30 cc orally, titrated to three to four stools daily

Q2: A 56-year-old chronic alcoholic has a 1-year history of ascites. He is admitted with a 2-day history of diffuse abdominal pain and fever. Examination reveals scleral icterus, spider angiomas, a distended abdomen with shifting dullness, and diffuse abdominal tenderness. Paracentesis reveals slightly cloudy ascitic fluid with an ascitic fluid PMN cell count of 1000/μL. Which of the following statements about treatment is true?

A- Antibiotic therapy is unnecessary if the ascitic fluid culture is negative for bacteria.
B- The addition of albumin to antibiotic therapy improves survival.
C- Repeated paracenteses are required to assess the response to antibiotic treatment.
D- After treatment of this acute episode, a second episode of spontaneous bacterial peritonitis would be unlikely.

Q3: A 70-year-old man presents with a complaint of fatigue. There is no history of alcohol abuse or liver disease; the patient is taking no medications. Scleral icterus is noted on physical examination; the liver and spleen are nonpalpable. The patient has a normocytic, normochromic anemia. Urinalysis shows bilirubinuria with absent urine urobilinogen. Serum bilirubin is 12 mg/dL, with 9.8 mg/dL direct-reacting fraction. Aspartate aminotransferase (AST) and alanine transaminase (ALT) are normal, and alkaline phosphatase (ALP) is 300 U/L (three times normal). Which of the following is the best next step in evaluation of this patient's jaundice?

A- Ultrasound or CT scan of the abdomen.
B- Viral hepatitis profile.
C- Reticulocyte count.
D- Antimitochondrial antibody.

Q4: A 47-year-old man presents complaining of weight gain, on examination there is an abdominal distension with a fluid thrill. Which of following is not a cause of ascites secondary to venous hypertension?

A- Congestive heart failure.
B- Cirrhosis.
C- Budd–Chiari syndrome.
D- Nephrotic syndrome.

Answers: Q1:D | Q2:B | Q3:A | Q4:D

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!