

## LIVER CIRRHOSIS

### Definitions:

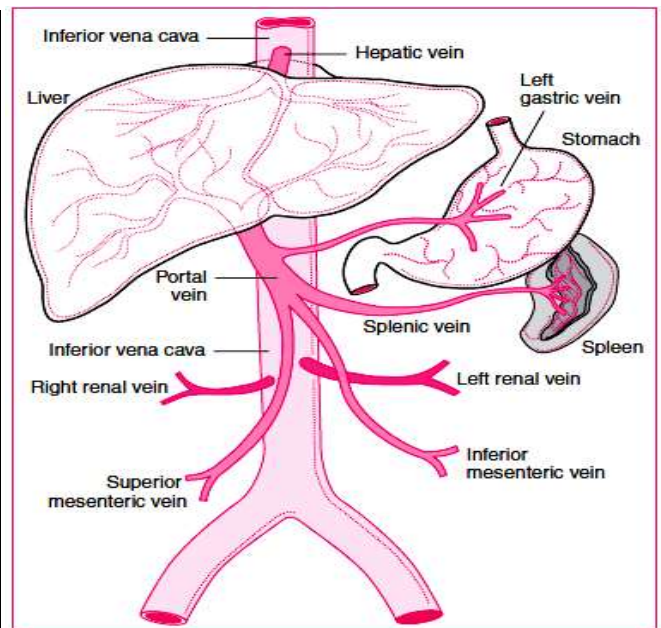
**Cirrhosis**, or end-stage liver disease, can be defined as **fibrosis of the hepatic parenchyma (hepatocytes) resulting in nodule formation with the consequent altered hepatic function, which results from a chronic or acute liver injury due to variable etiologies** <sup>(1)</sup>.

The word *cirrhosis* is derived from the Greek *kirrhos*, meaning orange-yellow, and refers to the color of the cirrhotic liver <sup>(2)</sup>.

### Etiology:

Cirrhosis has many causes (Table 1). World-wide, the most common etiologies of cirrhosis are chronic **viral hepatitis (types B and C)** and **prolonged excessive alcohol consumption** <sup>(2,3)</sup>.

Category	Example
Drugs and toxins	Alcohol, methotrexate, isoniazid, methyl dopa, organic hydrocarbons
Infections	<i>Viral hepatitis</i> (types B and C).
Metabolic	<i>Wilson's disease</i> (which cause deposition of copper in liver )
Cardiovascular	Chronic <i>right heart failure</i> (Liver is engorged with venous blood → cell anoxia → Cell necrosis )
Autoimmune	<i>Autoimmune hepatitis</i>



**Figure -1-The portal venous system**

### Pathophysiology:

The main pathophysiologic abnormalities that result from cirrhosis are <sup>(2)</sup>:

- 1-Ascites
- 2- Portal hypertension and esophageal varices
- 3- Hepatic encephalopathy
- 4-Spontaneous Bacterial Peritonitis
- 5- Hepatorenal syndrome
- 6-Coagulation defects

#### A-Ascites:

1- Ascites is the **accumulation of an excessive amount of fluids within the peritoneal cavity**. It is the **most commonly occurring** major complication of cirrhosis <sup>(2)</sup>.

2-The development of ascites is related to the **activation of the renin-angiotensin-aldosterone system (RAAS), with sodium and water retention** <sup>(1,2)</sup>.

3- Also the decrease in synthetic function leads to a **decrease in production of albumin (hypoalbuminemia)**. Albumin is the major protein involved in maintaining the *intravascular* oncotic pressure <sup>(4)</sup>. **Hypoalbuminemia and reduced plasma oncotic pressure also contribute to the loss of fluids from the intravascular compartment into the peritoneal cavity** <sup>(5)</sup>.

### **B-Portal hypertension and esophageal varices:**

1-Portal hypertension is a consequence of **increased resistance to blood flow through the portal vein** <sup>(2)</sup> **because of fibrotic changes within the hepatic sinusoids** <sup>(2)</sup>.

The most important sequel of portal hypertension are the **development of varices** and alternative routes of blood flow <sup>(2)</sup>.

**The varices** develop in the **esophagus, stomach, and rectum** to compensate for the increased blood volume (congested blood) <sup>(4)</sup>.

2-Varices are **weak superficial vessels**, and any additional increase in pressure can cause these vessels to **rupture and bleed** <sup>(4)</sup>. Hemorrhage from varices occurs in 25% -40% of patients with cirrhosis and is the cause of death for one third <sup>(2)</sup>.

### **C-Hepatic encephalopathy (HE):**

1- Serious complication of chronic liver disease and is broadly defined as an **alteration in mental status and cognitive function occurring in the presence of liver failure** <sup>(5)</sup>.

2- The symptoms of HE **range from forgetfulness, mental confusion, lethargy, personality changes, to somnolence, confusion, and coma** <sup>(6)</sup>.

3-The symptoms are thought to result from an accumulation of **gut-derived nitrogenous substances** in the systemic circulation. These substances have the ability to enter the CNS and result in alterations of neurotransmitters that affect consciousness and behavior <sup>(2)</sup>.

### **D-Spontaneous Bacterial Peritonitis (SBP)**

1-SBP is a common and severe *complication of ascites* and is defined as the **spontaneous infection of the ascitic fluid**. This condition has a mortality rate of about 30% to 50% <sup>(1,5)</sup>.

2-The primary mechanism for SBP is **bacterial translocation from the gut**. Cirrhosis can lead to **intestinal bacterial overgrowth** and the **intestinal wall permeability may be enhanced** in cirrhotic patients allowing gut bacteria to pass into ascitic fluid <sup>(1,4,5)</sup>.

3- **Enteric Gram-negative bacilli** (most commonly *Escherichia coli* and *Klebsiella Spps.* account for the majority of SBP episodes) <sup>(1)</sup>.

4- Patients **may be asymptomatic**, or may present with ***unexplained*** fever, or nonspecific abdominal pain <sup>(7)</sup>. (Further reading 1)

## E-Abnormalities in Coagulation

Most clotting factors are synthesized in the liver, and the levels of these factors can be significantly reduced in chronic liver disease. The net effect of the coagulation disorders that occur in cirrhosis is the ***development of bleeding tendency*** <sup>(2)</sup>.

## F- Hepatorenal syndrome

1-The hepatorenal syndrome (HRS) ***is a form of renal failure, but without renal pathology. This renal failure occurs in about 10% of patients with advanced cirrhosis or acute liver failure*** <sup>(5)</sup>.

2-**Type 1 HRS** is characterized by **progressive oliguria**, a **rapid rise of the serum creatinine** and a **very poor prognosis** <sup>(3)</sup>.

3-**Type 2 HRS** is **more slowly progressive and chronic** <sup>(8)</sup> and is associated **with a better outcome** than that of Type 1 HRS <sup>(5)</sup>.

## Signs and Symptoms

Cirrhosis is ***often asymptomatic until the late stages of disease*** <sup>(4)</sup>. The presenting signs and symptoms of cirrhosis are: <sup>(2)</sup>

- Hepatomegaly, splenomegaly.
- Pruritus, jaundice, palmar erythema, spider angiomas (*Vascular lesions consisting of a central arteriole surrounded by many smaller vessels*), hyperpigmentation.
- Gynecomastia, reduced libido.
- Ascites, bilateral leg edema, pleural effusion, and respiratory difficulties.
- Malaise, anorexia, and weight loss.
- Encephalopathy.

## Laboratory abnormalities <sup>(2)</sup>.

- **Hypoalbuminemia**
- **Elevated prothrombin time**
- **Thrombocytopenia**
- **Elevated alkaline phosphatase**
- **Elevated aspartate transaminase (AST), alanine transaminase (ALT), and  $\gamma$ -glutamyl transpeptidase.**

**Liver biopsy** plays a central role in the diagnosis and staging of liver disease.

# Treatment

## Desired Outcome <sup>(2)</sup>.

The desired therapeutic outcomes can be viewed in two categories:

- 1- **Prevention of complications.**
- 2- **Resolution of acute complications.**

## General approach:

**Primarily, any cause of cirrhosis should be identified and eliminated** (e.g., alcohol abuse) <sup>(2)</sup>.

### A-Hepatic Encephalopathy:

1-Treatment approaches include: **Reduction of blood ammonia concentrations** by:

- A-Inhibiting ammonia production or enhancing its removal (**lactulose** and **antibiotics**) <sup>(1)</sup>.
- B-Inhibition of  $\gamma$ -aminobutyric acid–benzodiazepine receptors by *flumazenil* <sup>(1)</sup>.

2-During episode of acute HE, temporary protein restriction to decrease ammonia production can be useful adjunctive measure to pharmacological therapy. Long term protein restriction is not recommended because *cirrhotic patients are already in a nutritional deficient state, and any further protein restriction on long term will exacerbate the problem* <sup>(4)</sup>.

3- *The use of lactulose is standard therapy for HE. Lactulose* metabolized by colonic bacteria to acetic and lactic acid; NH<sub>3</sub> present in the GI lumen is reduced to ammonium ion (NH<sub>4</sub><sup>+</sup>) through the reduction in pH and is therefore unable to diffuse back into the bloodstream.

**Dose:** 45 mL orally every 1–2 hours until the patient has a loose bowel movement; *then titrate to 2 or 3 loose bowel movements a day* (typically, a 15- to 45-mL dose 2–3 times/day) <sup>(9)</sup>.

4-**Antibiotic** therapy with **metronidazole** or **neomycin** is reserved for patients who have not responded to lactulose <sup>(2)</sup>. More recently, **rifaximin** has been very effective in treating encephalopathy **without the known side effects of neomycin or metronidazole** <sup>(5)</sup>. (Further reading 2)

5-**Zinc acetate supplementation** is recommended for long term management in patients with cirrhosis who are **zinc deficient** <sup>(2)</sup>.

### B-Spontaneous Bacterial Peritonitis (SBP):

1-Therapeutic antibiotics: *Patients with diagnosed or suspected SBP should receive broad-spectrum antibiotic* <sup>(2)</sup>. Examples of antibiotic:

**A-Third-generation cephalosporin:** Cefotaxime, 2 g every 8 hours I.V, or ceftriaxone 2 g/day I.V for 5 days is considered the drug of choice <sup>(2,9)</sup>.

**B-Fluoroquinolones** (ciprofloxacin or ofloxacin) may be used. **Oral ofloxacin**, 400 mg every 12 hours for 8 days, is equivalent to IV cefotaxime <sup>(2,8,9)</sup>.

**2-Albumin:** Plasma volume expansion with albumin in addition to antibiotics **decreases the incidence of hepatorenal syndrome** and improves survival <sup>(7)</sup>. (Further reading 3)

### 3-Prophylactic antibiotics:

A- **Primary prevention** (*prevention of SBP in patients who never develop SBP previously*) should be considered in all patients who are at high risk for this complication (e.g. those who experience a **variceal hemorrhage**) <sup>(2,9)</sup>.

Oral **norfloxacin** (400 mg orally twice a day) or intravenous **ceftriaxone** (1 g per day), which may be preferable, **for 7 days** reduces the risk of bacterial peritonitis in patients hospitalized for acute variceal bleeding <sup>(8)</sup>.

B-**Secondary prevention:** (*prevention of SBP in patients who do develop a previous infection*) :

**After SBP, there is a high probability of a further episode** <sup>(7)</sup>; therefore, all patients recovering from an initial episode of SBP should be treated with **oral** prophylactic antibiotics *indefinitely* <sup>(8)</sup>. Examples of antibiotic used for secondary prevention are **Norfloxacin, Trimethoprim-sulfamethoxazole and Ciprofloxacin** <sup>(4,7,8)</sup>.

(Further reading 4)

4-The patients should be considered for liver transplantation because 2-year survival is 25%–30% after recovery <sup>(9)</sup>.

### C-Management of Portal hypertension and Variceal Bleeding:

The management of varices involves three strategies <sup>(2)</sup>:

- (1) **Primary prophylaxis** to prevent bleeding
- (2) **Treatment** of active variceal bleeding.
- (3) **Secondary prophylaxis** to prevent rebleeding in patients who have already bled.

#### 1-Primary Prophylaxis (prevention of a first variceal bleeding)

A-Pharmacotherapy is not recommended to prevent the development of varices in patients with cirrhosis who have not yet developed varices <sup>(9)</sup>.

B-All cirrhotic patients who develop portal hypertension with **varices should receive primary prophylaxis with  $\beta$ -Adrenergic blockers to reduce portal pressure, thereby reducing the likelihood of variceal rupturing** <sup>(2)</sup>. (Further reading 5)

C-  $\beta$ -Adrenergic blocker therapy should be *continued for life*, because bleeding can occur when therapy is abruptly discontinued <sup>(1)</sup>.  
(Further reading 6)

## 2-Acute Variceal Hemorrhage

### 1-Fluid resuscitation:

Variceal hemorrhage is life-threatening; *rapid resuscitation with fluids and/or blood products are essential* <sup>(8)</sup>. (shock reduces liver blood flow and causes further deterioration of liver function) <sup>(3)</sup>.

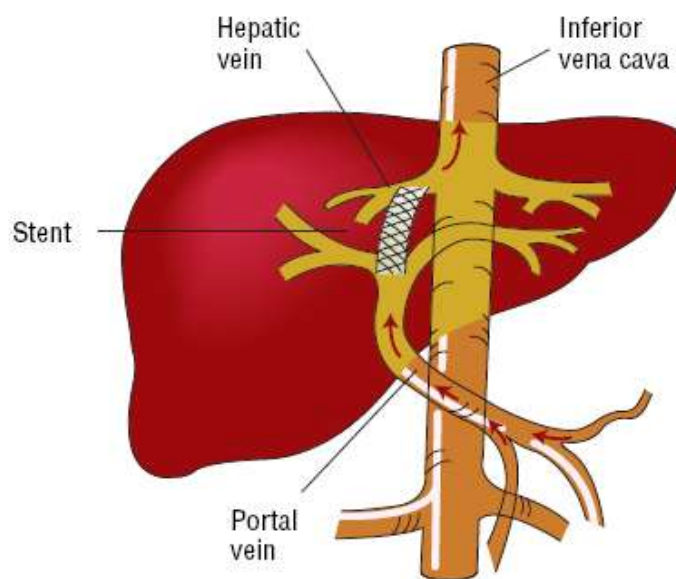
**2-Combination pharmacologic therapy plus endoscopic variceal ligation (EVL) or sclerotherapy (when EVL is not technically feasible) is the most rational approach to treatment of acute variceal bleeding** <sup>(2)</sup>. (Further reading 7)

**3- Vasoactive drug therapy (somatostatin, octreotide (a synthetic analogue of somatostatin), or terlipessin).** These agents decrease splanchnic blood flow and reduce portal and variceal pressures, without significant adverse effects <sup>(4)</sup>. Therapy may continue for 2 to 5 days since <sup>(7)</sup> (this is the time frame during which the risk of rebleeding is highest) <sup>(4)</sup>.

**4- Prophylactic acid suppression with proton pump inhibitors** reduces the risk of secondary bleeding which may result from EVL-induced ulcers <sup>(3)</sup>.

**5-All patients with cirrhosis and gastrointestinal bleeding should receive prophylactic antibiotics, because sepsis is common and treatment with antibiotics has been shown to improve outcome** <sup>(3)</sup>.

**6-If standard therapy fails to control bleeding, an invasive procedure such transjugular intrahepatic portosystemic shunt (TIPS) is done.** The TIPS procedure involves the placement of one or more stents between the hepatic vein and the portal vein <sup>(1)</sup> (figure 2).



**Figure 2: TIPS**

### 3-Prevention of rebleeding (secondary prophylaxis):

**A-All patients with a history of variceal bleeding should receive secondary prophylaxis to prevent recurrent bleeding** <sup>(9)</sup>.

**B- A combination of EVL and nonselective  $\beta$ -blockers (Propranolol or nadolol) is considered the most effective regimen** <sup>(9)</sup>.

**C-The combination therapy of a nonselective  $\beta$ -blocker with isosorbide mononitrate can be used in patients unable to undergo EVL** <sup>(2)</sup>.

D-Patients who cannot tolerate or who fail pharmacologic and endoscopic interventions **can be considered for TIPS to prevent rebleeding** <sup>(2)</sup>.

## D-Ascites:

1-For patients with ascites, a **serum-ascites albumin gradient (SAAG)** (serum albumin minus ascitic albumin) should be determined <sup>(6)</sup>.

The SAAG can accurately determine whether ascites is a result of portal hypertension or another process [*If the SAAG is greater than 1.1 g/dL, the patient almost certainly has portal hypertension and ascites will usually respond to salt restriction and diuretics. If the SAAG is less than 1.1 g/dL, the patient likely does not have portal hypertension and is less likely to respond to these measures*] <sup>(2)</sup>.

2-The treatment of ascites includes **abstinence from alcohol, sodium restriction, and diuretics**. Sodium chloride should be restricted to 2 g/day <sup>(2)</sup>.

If sodium restriction alone fails to result in diuresis and weight loss, diuretics should be prescribed <sup>(4)</sup> with a goal of **0.5-kg maximum daily weight loss** <sup>(2)</sup>.

Because of the role of hyperaldosteronism in ascites, **spironolactone** is the diuretic of 1<sup>st</sup> choice. Loop diuretics (**furosemide**) may be added to the regimen <sup>(1, 8)</sup>. Diuretic therapy in cirrhosis is typically **lifelong** <sup>(4)</sup>. (**Further reading 8**)

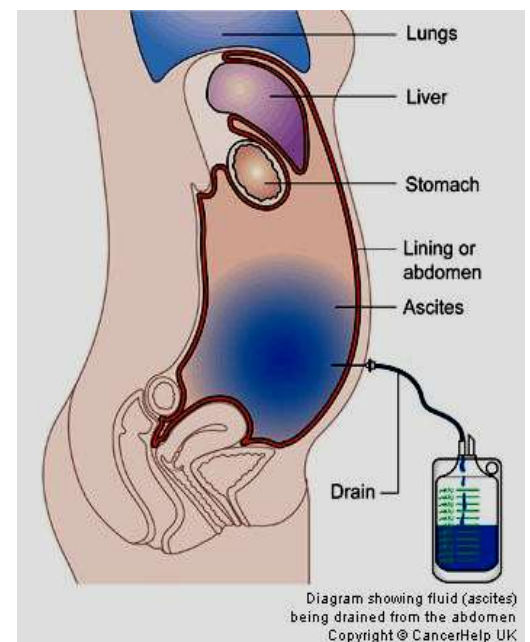
3-In patients with **pronounced** ascites or **resistant** to maximum doses of diuretics, **paracentesis** (removal of ascitic fluid from the abdominal cavity with a needle or a catheter) has proven to be an effective treatment <sup>(10)</sup>.

**Concomitant albumin** replacement by intravenous infusion is given to avoid depleting the intravascular space from this protein and precipitating hypotension because ascites fluid drained via paracentesis is rich in albumin <sup>(4)</sup>.

4-**TIPS** (see above) or **Liver transplantation** should be considered in patients with refractory ascites <sup>(2)</sup>.

## E-Pruritus:

1-Antihistamines are not very effective for pruritus in liver disease. If given, non-sedating antihistamines would be preferable (e.g. **loratidine**), as **sedating antihistamines could mask the symptoms of hepatic encephalopathy** <sup>(10)</sup>.



2-Anion exchange resins (**colestyramine**) bind to the bile acids that cause itching and is first-line therapy <sup>(10)</sup>.

### **F-Clotting disorders:**

Treatment is vitamin K (phytomenadione), 10 mg given IV for 3 days. The patient's INR and prothrombin time are monitored <sup>(4)</sup>.

### **G-Hepatorenal syndrome:**

1- *Precipitating factors such as infection (SBP), fluid loss, and blood loss* should be investigated and treated appropriately <sup>(2)</sup>.

2-*The definitive treatment for HRS is liver transplantation*, which is the only treatment that assures long-term survival. The main goal of pharmacologic therapy is to reverse HRS sufficiently so that patient can survive until suitable donor organs available <sup>(1)</sup>.

3-**Diuretic therapy must be stopped** because this can worsen the kidney disease <sup>(1)</sup>.

4-Management of hepatorenal syndrome also includes **expanding the intravascular volume with intravenous albumin** <sup>(2)</sup> **plus vasoconstrictors** [either terlipressin or ( $\alpha$ -agonist midodrine – octreotide combination)] <sup>(7)</sup>.

### **Liver Transplantation**

Liver transplantation in cirrhosis is considered in patients **with severe, irreversible liver disease** <sup>(1)</sup>. Liver transplantation is the **only treatment that can offer a cure for complications of end-stage cirrhosis** <sup>(2)</sup>.

The **outcome of Liver transplantation in cirrhosis is good**, with an overall survival rate of 70-85% <sup>(11)</sup>.

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## Further Reading (إلاطلاع)

1- The diagnosis of SBP is defined by a polymorphonuclear cell count (PMN) of greater than or equal to 250 cells/ $\mu$ L of the ascitic fluid **or a positive bacterial culture of the ascitic fluid** <sup>(1)</sup>.

2-The **alternating administration** of neomycin and metronidazole has commonly been employed to reduce the individual side effects of each: *neomycin for renal insufficiency and ototoxicity* and *metronidazole for peripheral neuropathy*.

3-Patients with cirrhosis have a state of intravascular hypovolemia and organ hypoperfusion; SBP is thought to enhance this effect, resulting in progressive renal hypoperfusion and precipitation of renal failure or hepatorenal syndrome <sup>(9)</sup>. Recent guidelines suggest using this albumin regimen with antibiotics if SCr is more than 1 mg/dL, BUN more than 40 mg/dL, or total bilirubin more than 4 mg/dL <sup>(9)</sup>.

4- Examples of antibiotic used for secondary prevention are:

-**Norfloxacin** (400 mg PO daily) <sup>(4,7)</sup>.

-**Trimethoprim-sulfamethoxazole** (single dose of 2 tablet) **5 days per week** (Monday through Friday) <sup>(4,8)</sup>.

-**Ciprofloxacin** 750 mg **once weekly** <sup>(4,7)</sup>.

5-These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: Blockade of  $\beta$ 1-receptors reduces cardiac output, whereas blockade of  $\beta$ 2-receptors prevents splanchnic vasodilation; unopposed  $\alpha$ 1-mediated constriction of the splanchnic circulation also leads to reductions in portal pressure <sup>(9)</sup>.

6-Therapy should be initiated with **propranolol**, 10 mg thrice daily <sup>(1)</sup>( or 20 mg twice daily) <sup>(2)</sup>, or **nadolol**, 20 mg once daily <sup>(1)</sup>( or 40 mg once daily) <sup>(2)</sup>, and titrated to a reduction in **resting heart rate of 20-25% of the baseline, or an absolute heart rate of 55 -60 beats/min** <sup>(1)</sup>.

7- **EVL** involves the varices being sucked into a cap placed on the end of the endoscope, allowing them to be occluded with a tight rubber band. The occluded varix subsequently sloughs with variceal obliteration. EVL has fewer side-effects than sclerotherapy <sup>(3)</sup> (injection of a sclerosing agent into the lumen of the varices) <sup>(2)</sup>.

8- Thus, spironolactone is initially given at a dose of 100 mg/d with or without furosemide, 40 mg/d, and both agents may be increased (every 3–5 days) by 100- and 40-mg increments respectively <sup>(1,8)</sup> (i.e. maintaining the 100:40 mg ratio) <sup>(2)</sup> (**This ratio usually maintains serum potassium concentrations within the normal range**) <sup>(4)</sup> to a maximum daily dose of 400 mg spironolactone and 160 mg furosemide <sup>(2)</sup>.

