Cirrhosis

Cirrhosis is a diffuse injury to the liver characterized by fibrosis and a conversion of the normal hepatic architecture into structurally abnormal nodules. The end result is destruction of hepatocytes and their replacement by fibrous tissue.

The resulting resistance to blood flow results in portal hypertension and the development of varices and ascites. Hepatocyte loss and intrahepatic shunting of blood result in diminished metabolic and synthetic function, which leads to hepatic encephalopathy and coagulopathy.

Causes of Cirrhosis:

Alcohol consumption	
Chronic viral hepatitis	• Viral hepatitis types B • Viral hepatitis types C
Metabolic liver disease	• Hemochromatosis • Wilson disease • α1-antitrypsin deficiency • Nonalcoholic steatohepatitis • Cystic fibrosis
Immunologic disease	• Autoimmune hepatitis • Primary biliary cirrhosis
Vascular disease	• Budd–Chiari syndrome • Heart failure
Drugs	• Isoniazid • Methyldopa • Amiodarone • Methotrexate • Tamoxifen • Retinol (*vitamin A*) … etc.

Hepatic Fibrosis

All chronic liver diseases that progress to cirrhosis have in common the histologic features of hepatic fibrosis and nodular regeneration. However, the patients' signs and symptoms may vary, depending on the underlying etiology of the disease.

Signs and symptoms

Cirrhosis can be asymptomatic. The following signs and symptoms can be noticed:

- Hepatomegaly and splenomegaly
- Pruritus and jaundice
- Palmar erythema, spider angiomata and hyperpigmentation
- Gynecomastia and reduced libido
- Ascites, edema, pleural effusion, and respiratory difficulties
- Malaise, anorexia and weight loss
- Encephalopathy

Laboratory tests

- Hypoalbuminemia
- Elevated prothrombin time (PT)
- Thrombocytopenia
- Elevated alkaline phosphatase (AST)
- Elevated aspartate transaminase, alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT)

Complications of Cirrhosis

Cirrhosis results in elevation of portal blood pressure because of fibrotic changes within the hepatic sinusoids, changes in the levels of vasodilatory and vasoconstrictor mediators, and an increase in blood flow to the splanchnic vasculature.
The pathophysiologic abnormalities that cause it result in the following problems:

- Ascites
- Portal hypertension
- Esophageal varices
- Hepatic encephalopathy
- Coagulation disorders
- Others…

1. Ascites

Ascites is the pathologic accumulation of lymph fluid within the peritoneal cavity. It is one of the earliest and most common presentations of cirrhosis.

The development of ascites is related to systemic arterial vasodilation that leads to the activation of the baroreceptors in the kidney and an activation of the renin–angiotensin–aldosterone system, activation of the sympathetic nervous system, and release of antidiuretic hormone in response to the arterial hypotension. These changes cause sodium and water retention.

For patients with ascites, a serum-ascites albumin gradient should be determined. If it is greater than or equal to 1.1 g/dL, the patient almost certainly has portal hypertension.

Treatment:

- ***Diuretic*** therapy should be initiated with single morning doses of spironolactone and furosemide.
- Other diuretics that may be used include amiloride, triamterene, or ethacrynic acid.
- The treatment of ascites secondary to portal hypertension includes abstinence from alcohol, sodium restriction and diuretics.
- Water restriction is used only if persistent hyponatremia is present.
- Liver transplant should be considered in patients with refractory ascites.

Monitoring

The best method of assessing the effectiveness of diuretic therapy is by monitoring body weight and urinary sodium levels.

In general, the goal of diuretic treatment of ascites should be to achieve a weight loss of 300-500 g/d in patients without edema and 800-1000 g/d in patients with edema.

Once ascites has disappeared, diuretic treatment should be adjusted to maintain the patient free of ascites.

2. Portal hypertension

Portal hypertension is defined by the presence of a gradient of greater than 5 mmHg between the portal and central venous pressures. Portal hypertension results from a combination of increased portal venous inflow and increased resistance to portal blood flow.

Portal hypertension causes blood flow to be forced backward, causing veins to enlarge and varices to develop across the esophagus and stomach from the pressure in the portal vein. The backup of pressure leads to splenomegaly.

Portal hypertension is characterized by hypervolemia, increased cardiac index, hypotension and decreased systemic vascular resistance.

Causes of portal hypertension

Prehepatic causes	splenic vein thrombosis portal vein thrombosis	
Intrahepatic causes	Presinusoidal conditions	
	Sinusoidal conditions	**Cirrhosis**
	Postsinusoidal conditions	
Posthepatic causes	chronic right-sided heart failure	
	tricuspid regurgitation and obstructing lesions of the hepatic veins and inferior vena cava	

Treatment:

All patients with cirrhosis and portal hypertension should be screened for varices on diagnosis.

The mainstay of primary prophylaxis is the use of a nonselective β-adrenergic blocking agent such as propranolol or nadolol.

In case of contraindications or intolerance to therapy with nonselective β-adrenergic blockers, patient should be considered for alternative prophylactic therapy with ***endoscopic variceal ligation*** (EVL).

The vasoconstrictors somatostatin and octreotide are used to treat acute bleeding in patients with portal hypertension before performing endoscopy.

Vasodilators such as isosorbide mononitrate (ISMN) reduce intrahepatic vascular resistance without decreasing the peripheral or portal-collateral resistance.

3. Esophageal varices

The most important sequelae of portal hypertension are the development of varices and alternative routes of blood flow resulting in acute variceal bleeding.
Variceal hemorrhage is a complication.

Treatment:

The goals of treatment of variceal hemorrhage include:

- Adequate blood volume resuscitation
- Protection of the airway from aspiration of blood
- Prophylaxis against *spontaneous bacterial peritonitis* (SBP) and other infections
- Correction of significant coagulopathy and thrombocytopenia with fresh frozen plasma and platelets, control of bleeding and prevention of rebleeding,
- Preservation of liver function.

Combination pharmacologic therapy plus EVL or sclerotherapy is the most rational approach to treatment of acute variceal bleeding. *Sclerotherapy is a medical procedure used to eliminate varicose veins and spider veins.*

Vasoactive drug therapy (usually **octreotide**) to stop or slow bleeding is routinely used early in patient management to allow stabilization of the patient.

Vasopressin, alone or in combination with nitroglycerin, is not recommended as first line therapy. Vasopressin is used off-label for the management of acute variceal bleeding.

Terlipressin is a synthetic analogue of vasopressin. It is widely used in Europe. It is the only pharmacologic agent shown to reduce mortality from variceal bleeding. It has longer biologic activity than vasopressin. The drug is beneficial when combined with sclerotherapy. Terlipressin also has the advantage of preserving renal function, which is a particularly important feature in patients with cirrhosis.

Antibiotic therapy should be used early to prevent sepsis in patients with signs of infection or ascites.

A nonselective β-adrenergic blocker (propranolol or nadolol) along with EVL is the best treatment option for prevention of **rebleeding**. The combination therapy of a nonselective β-blocker with ***isosorbide mononitrate*** can be used in patients unable to undergo EVL.

4. Hepatic encephalopathy

Hepatic encephalopathy is a metabolically induced functional disturbance of the brain that is potentially reversible.

The symptoms of hepatic encephalopathy are resulted from an accumulation of gut-derived nitrogenous substances in the systemic circulation. These substances then enter the central nervous system and result in alterations of neurotransmission that affect consciousness and behavior.

Altered ammonia, glutamate, benzodiazepine receptor agonists, aromatic amino acids, and manganese are potential causes of hepatic encephalopathy.

Types of hepatic encephalopathy:

- Type A is induced by acute liver failure
- Type B results from portal-systemic bypass without intrinsic liver disease
- Type C occurs with cirrhosis.

Hepatic encephalopathy may be classified as episodic, persistent or minimal.

Treatment:

- Reduction in blood ammonia concentrations by dietary restrictions, with drug therapy aimed at inhibiting ammonia production or enhancing its removal (**lactulose** and antibiotics).
- Inhibition of γ-aminobutyric acid-benzodiazepine (GABA) receptors by **flumazenil**.
- **Zinc acetate** supplementation is recommended for long-term management in patients with cirrhosis who are zinc deficient. Zinc is effective in the treatment of muscle cramps and is adjunctive therapy for hepatic encephalopathy.
- **Bromocriptine** is indicated for chronic hepatic encephalopathy in patients who are unresponsive to other treatments.
- **Rifaximin** plus lactulose is more effective than lactulose as monotherapy. Rifaximin should be added on to lactulose in recurrent hepatic encephalopathy following second recurrence. Rifaximin can decrease colonic levels of ammoniagenic bacteria, with resulting improvement in the symptoms of hepatic encephalopathy.
- Antibiotic therapy with neomycin and other antibiotics (e.g., metronidazole, oral vancomycin, paromomycin, oral quinolones) serve as second-line agents for patients who have not responded to diet and lactulose.
- Other chemicals capable of decreasing blood ammonia levels are L-ornithine L-aspartate and sodium benzoate.

5. Coagulation Defects

Complex coagulation derangements can occur in cirrhosis. These derangements include the reduction in the synthesis of coagulation factors, excessive fibrinolysis, disseminated intravascular coagulation, thrombocytopenia and platelet dysfunction.

Vitamin K–dependent clotting factor levels are decreased, with factor VII affected first because it has a short half-life. The net effect of these events is the development of bleeding diathesis.

Treatment:

Patients with liver disease who develop deranged blood clotting should receive intravenous doses of **phytomenadione** (vitamin K).

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants should be avoided in all patients with liver disease because of the risk of altering platelet function, causing gastric ulceration and bleeding.

Most hepatologists permit the use of paracetamol in patients with cirrhosis at doses of up to 2000 mg daily.

6. Pruritus

Pruritus is a common complaint in liver diseases, mostly in cholestatic liver diseases such as primary biliary cirrhosis and sclerosing cholangitis, although it is also common in persons with hepatitis C virus (HCV)–related cirrhosis.

Mild itching complaints may respond to treatment with antihistamines and topical ammonium lactate.

Pruritus responds to sequential therapy with use of antihistamines, ursodeoxycholic acid, and cholestyramine. Cholestyramine is the mainstay of therapy for the pruritus of liver disease.

Opiate antagonists (eg, naloxone, nalmefene, naltrexone) have increasingly been used in the treatment of refractory pruritus.

7. Hepatorenal Syndrome (HRS)

Hepatorenal syndrome is defined as a deterioration of renal function in a patient with advanced cirrhosis, with a creatinine level of more than 1.5 mg/dL, a urine volume of less than 500 mL/d, and a low producing urinary sodium level (< 10 mEq/L).

There are two types of HRS:

- ***HRS type 1*** is rapidly progressive, necessitating dialysis and producing rapid deterioration that is responsive only to emergency transplantation.
- ***HRS type 2*** is more indolent, with minor elevation of creatinine.

Hepatorenal syndrome represents a continuum of renal dysfunction that may be observed in patients with a combination of cirrhosis and ascites. Hepatorenal syndrome is caused by the vasoconstriction of large and small renal arteries and the impaired renal perfusion that results.

NSAIDs inhibit prostaglandin synthesis. They may potentiate renal vasoconstriction, with a resulting drop in glomerular filtration. Thus, the use of NSAIDs is contraindicated in patients with decompensated cirrhosis.

Nephrotoxic medications, including aminoglycoside antibiotics, should be avoided in patients with cirrhosis.

Patients with early hepatorenal syndrome may be salvaged by aggressive expansion of intravascular volume with albumin and fresh frozen plasma and by avoidance of diuretics.

8. Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis (SBP) is now known to affect patients with cirrhosis from any cause. In addition, spontaneous bacterial peritonitis can occur as a complication of any disease state that produces the clinical syndrome of ascites, such as heart failure and *Budd-Chiari syndrome*. Children with nephrosis or systemic lupus erythematosus who have ascites have a high risk of developing spontaneous bacterial peritonitis.

Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy to cover *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*.

Treatment:

The goals of pharmacotherapy in patients with spontaneous bacterial peritonitis (SBP) are to reduce morbidity and prevent complications. Antibiotics are initially chosen empirically. A 10- to 14-day course of antibiotics is recommended and directed mostly toward gram-negative enteric organisms, should be started early.

Treatment options are:

- Rifaximin is commonly used, with or without a concomitant quinolone.
- Cefotaxime, 2 g every 8 hours, or a similar third-generation cephalosporin for 5 days is considered the drug of choice.
- Oral ofloxacin is an alternative. Ampicillin is another choice. Gentamicin may be used.

Prophylaxis

- Ciprofloxacin, norfloxacin or trimethoprim-sulfamethoxazole.
- Probiotic therapy in conjunction with antimicrobial treatment does not improve efficacy in the treatment of spontaneous bacterial peritonitis.

Liver transplantation

Liver transplantation is the established treatment for selected patients with acute liver disease, decompensated chronic liver disease, inherited metabolic disorders and primary liver cancer. HCV and alcohol-induced end-stage liver disease are the commonest indications for liver transplantation in Europe and the USA.

In case of a potential candidate for liver transplantation, the patient's degree of illness and overall suitability for liver transplantation should be determined by 2 steps:

1. establishment a diagnosis of end-stage liver disease (ESLD) by clinical evaluation;
2. exclusion of any absolute or relative contraindication to liver transplantation.

Remarkably few transplants fail because of rejection and, nowadays, technical problems, infection and multisystem failure account for most deaths in the first year.

The calcineurin inhibitors (**tacrolimus** and **ciclosporin**) remain the mainstay of immunosuppressive therapy. Corticosteroids are still commonly used, at least during the first 3 months after transplantation.

The other drugs used regularly for long-term immunosuppression include ***azathioprine***, ***mycophenolate mofetil***, and mTOR inhibitors (***sirolimus*** and ***everolimus*****)**.

Basiliximab is used in the prophylaxis of acute liver transplant rejection.

Potential candidacy for liver transplantation:

- *Cirrhosis from hepatitis B or C*
- *Non-alcoholic steatohepatitis (NASH)*
- *Cholestatic liver diseases (ie, primary biliary cirrhosis, secondary biliary cirrhosis, primary sclerosing cholangitis)*
- *Biliary atresia*
- *Acute hepatic failure, including acutely decompensated Wilson disease*
- *Metabolic diseases (ie, alpha-1-antitrypsin deficiency, Wilson disease, tyrosinemia, glycogen storage disorder type I or type IV)*
- *Malignant neoplasms or benign tumors (ie, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, polycystic liver disease, hepatic adenoma)*
- *Cystic fibrosis*
- *Budd-Chiari syndrome*
- *Total parenteral nutrition/hyperalimentation*
- *Neonatal hepatitis*
- *Congenital hepatic fibrosis*
- *Byler disease*
- *Trauma*
- *Graft versus host disease*