4 Pathophysiology of Chronic Liver Disease

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4.1 Introduction

The liver being the largest solid organ in the human body is affected by many different pathogenic agents and processes. Increasing incidence of liver disease is primarily driven by lifestyle factors (alcohol, obesity) and infection of the liver parenchyma. Liver diseases can be manifested in a number of ways, which may be acute or chronic, focal or diffuse, mild or severe. Acute liver disease is a self-limiting disease in which symptoms do not persist beyond 6 months. Most cases are due to episodes of hepatocyte inflammation or damage, which resolve without causing any further complications. Mostly the manifestation of acute liver disease (e.g., viral hepatitis) is so mild that they never come to medical attention. However the entire liver may be affected in few cases leading to fulminant liver failure, which is a life-threatening condition. In chronic liver disease the symptoms persist for more than 6 months. It occurs because of permanent structural damage to the liver architecture as a result of continued inflammation of the hepatocytes after the primary insult. Cirrhosis is the ultimate consequence of progressive liver injury. Cirrhosis develops in a subset of cases of chronic liver disease and may be a consequence of repeated episodes of acute liver injury. Cirrhosis is manifested as a grossly impaired liver function due to decrease amount of functional liver tissue. Change in liver architecture leads to change in the physics of blood flow in and around the liver. Elevation in portal vein pressure diverts blood away from the liver causing portosystemic shunting, which has a profound effect on functioning of various organ systems.

Understanding of the liver parenchymal arrangement and blood flow is critical to the understanding of the liver inflammation.

4.2 Cellular Anatomy of the Liver

The liver is the largest organ in the human body and is located in the right upper quadrant of the abdomen. The liver receives around 25% of the cardiac output from the portal vein and the hepatic artery [1]. The blood flow exits the liver via the central veins which drains into the hepatic vein and finally to the inferior vena cava [2].

The liver parenchyma consists of hepatocytes, which are organized into plate of hepatocytes, and is supported by reticuloendothelial cells. These one-cell-thick plates of hepatocytes are separated from each other by vascular spaces called sinusoids. The blood from the portal vein and the hepatic artery is mixed in these sinusoids while flowing toward the central vein. The reticuloendothelial cells, which consist approximately 30% of

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all cells of the liver, have diverse types of cells [2]. Endothelial cells (makes the boundary of the sinusoids), Kupffer cells (specialized macrophages), and stellate cells (fat storing cells) are the most important cell types in the reticuloendothelial cell meshwork. These cells perform specific functions by communicating with each other and with the hepatocytes. Dysfunction of these cells leads to different grades of inflammations, starting from necrosis of hepatocytes in acute liver diseases to fibrosis in chronic liver disease and cirrhosis.

Liver architecture has been traditionally described in terms of the lobule. In a lobule arrays of hepatocyte plates are organized in the form of a hexagon around a central vein with portal triads at the corners of the hexagon. The portal triad consists of a bile canaliculus, portal venule, and hepatic arteriole. The hepatocytes adjacent to the portal triad consist of the limiting plate and disruption of this is a significant marker of some immune-mediated liver disease [2].

4.3 Etiology of Chronic Liver Disease

Many different pathogenic agents and processes cause chronic liver disease. These etiologies can be simply classified as per Table 4.1.

Although many factors contribute toward the development of chronic liver disease, they ultimately lead to development of cirrhosis. The three common model of hepatic injury are the: alcoholic-induced model, post viral hepatitis model, and drugs- and toxin-induced model.

Table 4.1 Chronic liver failure etiology

Etiology of chronic liver failure	
Common causes:	Lesser common causes:
• Alcohol	• Drug and toxin induced
• Chronic viral hepatitis (B and C)	• Autoimmune chronic hepatitis (1, 2, and 3)
• Biliary obstruction	• Genetic and metabolic disease
– Biliary atresia	• Infection
– Cystic fibrosis	• Idiopathic
• Primary and secondary biliary cirrhosis	• Veno-occlusive disease
• Nonalcoholic fatty liver diseases (NAFLD)	• Vascular abnormalities
• Hemochromatosis	• Miscellaneous

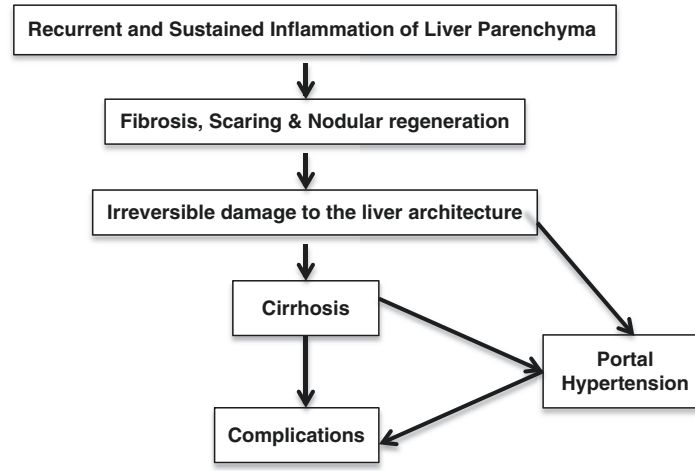
4.4 Pathophysiology of Chronic Liver Disease

Irrespective of the etiology the path of progression of a liver injury to chronic liver injury follows a similar flow, which is demonstrated in Flow Diagram 4.1.

4.4.1 Basics of Liver Inflammation

The classical picture of any insult to the liver is inflammation and damage leading to production of stressed hepatocytes. Persistent and recurrent injuries ultimately lead to hepatic fibrosis, which is the common end point for most of the chronic liver disease. Normally the liver eliminates the cellular debris produced by the inflammation and tries to restitute the cellular integrity by regeneration. However when the liver fails to maintain this sequence of elimination and regeneration, inflammation continues and fibrosis follows. When the fibrosis becomes an irreversible process, then the cirrhosis sets in.

Different types of disease may lead to different patterns of fibrosis during disease progression. Histology shows predominance of different fibrogenic cells in different types of fibrosis [3, 4]. Chronic infection of the liver caused by hepatotropic viruses follows a classic pattern of inflammation, the death of hepatocytes, and finally liver fibrosis [5] whereas alcoholic hepatitis and nonalcoholic steatohepatitis are associated with a change in hepatocyte lipids on histology, hepatocyte ballooning/necrosis, neutrophil infiltration, and the development of a particular type of fibrosis. Chronic or persistent obstruction of the biliary tree leads to hepatocyte necrosis and to lobular bile infarcts due to extensive proliferation of periductular fibroblasts [6].



Flow Diagram 4.1 Pathophysiology of chronic liver disease

4.4.2 Cells Involved in Liver Inflammation

Hepatocytes constitute 70–80% of the cytoplasmic mass of the liver and have an average life span of 5 month, with the ability to regenerate [7]. Hepatocytes are responsible for most of the functions of the liver. They are also responsible for the synthesizing cytokines, acute phase proteins like C-reactive protein (CRP) or serum amyloid A (SAA), and many others during an acute phase [8, 9]. These cells also possess different intracellular defense mechanism to combat any acute insult. However when these defense mechanisms are not sufficient to withstand, the damaging cells start to synthesize chemokines, which are supposed to be responsible for attraction of inflammatory cells like granulocytes and mononuclear phagocytes and activation of resident macrophages. In this attempt to eliminate the damage, the defense response however leads to death of the stressed hepatocyte.

Hepatic stellate cells (HSC) have a very important role as they modulate the inflammatory conditions, based on their capability of cytokine and chemokine production.

Hepatic stellate cells might also play a role during liver inflammation by modulating the recruitment and migration of mononuclear cells within the perisinusoidal space of diseased livers.

Sinusoids display a discontinuous, fenestrated endothelial cell lining. The sinusoidal "wall" does not possess a basement membrane and the endothelial cells are separated from the hepatocytes by the space of Disse which drains lymph into the portal tract lymphatics [7]. During inflammation the chemokine expression profile of the normal hepatic endothelium changes. Similarly to the chemokine profile the expression pattern of adhesion molecules also changes in the endothelial cells.

Kupffer cells are scattered within the liver sinusoid; they are a major part of the reticuloendothelial system and phagocytose spent erythrocytes. Kupffer cells are the specialized macrophages of the liver that form a major part of the reticuloendothelial system (mononuclear phagocyte system) [10].

Activation of Kupffer cells results in secretion of a large number of chemical mediators, most of which can induce liver injury either by acting directly on the liver cells or via chemoattraction of extrahepatic cells (e.g., neutrophils and lymphocytes). The chemical mediators released by Kupffer cells and by hepatocytes attract extrahepatic cells to the liver. Neutrophils (PMN) are the characteristic cellular compound of the chemoattracted cells and are involved in acute inflammation. They are always present in the inflammatory infiltrate of chronic liver disease. However, neutrophil infiltration is most prominent in alcoholic

hepatitis. Up to now the role of T lymphocytes in liver disease is still ill-understood.

Hepatocellular stress (induced by toxins or infections) leads to activation of macrophages in the liver parenchyma and release of proinflammatory chemokines and cytokines from various cell types in the liver. This leads to recruitment and sinusoidal transmigration of inflammatory cells toward the target hepatocyte. Inflammation persists as long as the damaging stimulus persists or are repeatedly exposed. The hepatic infiltrate includes granulocytes, macrophages, T lymphocytes, B lymphocytes, and plasma cells. The inflammatory macrophages activate the mesenchymal cells and stimulate the synthesis of matrix with the help of cytokines and growth factors.

4.4.3 Repair of the Damaged Liver

The processes of liver repair and fibrogenesis resemble that of a wound-healing process. Following injury and acute inflammation response takes place resulting in moderate cell necrosis and extracellular matrix damage. After that tissue repair takes place where dead cells are replaced by normal tissue with regeneration of specialized cells by proliferation of surviving ones or generation from stem cells, formation of granulation tissue, and tissue remodeling with scar formation [4].

Recurrent or chronic, injury or insult give way to excess matrix deposition as a result of an imbalance between fibrogenesis and fibrolysis leading to scar formation. The high rate of tissue destruction with slow regeneration also provides the space for matrix deposition. Liver fibrosis is a common sequel to diverse liver injuries such as chronic viral hepatitis, ethanol, biliary tract diseases, iron or copper accumulation. As scarring progresses from bridging fibrosis to the formation of complete nodules it results in an architectural distortion and ultimately in liver cirrhosis [11].

Liver fibrosis is defined as an abnormal accumulation of extracellular matrix in the liver. Its end point is liver cirrhosis which is responsible for significant morbidity and mortality. Cirrhosis is an advanced stage of fibrosis, characterized by the formation of regenerative nodules of liver parenchyma separated by fibrotic septa, which result from cell death, aberrant extracellular matrix deposition, and vascular reorganization. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation [11].

Accumulating data from clinical and laboratory studies demonstrate that even advanced fibrosis and cirrhosis are potentially reversible. The hepatic stellate cells have been identified as the pivotal effector cells orchestrating the fibrotic process and, furthermore, reversibility appears to hinge upon their elimination. Removing the insult and stopping the persistent inflammatory stimuli is probably the best way to prevent progression of fibrosis; nevertheless, prevention of the progression of fibrosis to cirrhosis remains the major clinical goal. The poor prognosis of cirrhosis is aggravated by the frequent occurrence of hepatocellular carcinoma.

4.5 Cirrhosis and Portal Hypertension

Cirrhosis is the end product of steady or recurrent episode of liver parenchymal inflammation leading to necrosis and disruption of normal hepatic architecture. The normal liver is replaced by advanced fibrosis, scaring, and formation of regenerative nodules. These changes in liver architecture lead to change in blood flow in and around the liver. Increase resistance to blood flow results in the formation of shunts between the afferent and efferent vessels and increase in portal venous pressure. The resulting portal hypertension can be quantified by measuring the hepatic venous pressure gradient (HVPG). Portal hypertension is present if HVPG is >5 mmHg; however it is clinically significant if it is >10–12 mmHg. The buildup of portal hypertension is a turning point in the pathophysiology of CLD as at this point the CLD becomes a systemic disease, affecting other organ systems as well. Portal hypertension contributes to the pathogenesis of cirrhosis and its complications by formation of

venous collaterals, increase production of biochemical (vasoconstrictors, splanchnic vasodilators, nitric oxide and others) and other functional abnormalities (expansion of plasma volume, increased cardiac output, etc.) [12, 13].

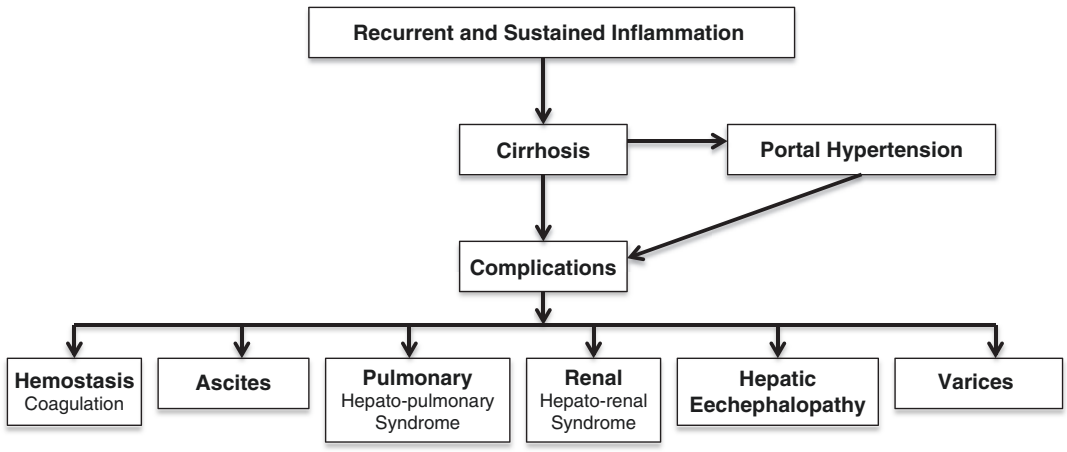
The complications of cirrhosis occur secondary to portal hypertension, abnormal synthetic function, or combination of both. Major complications of cirrhosis and portal hypertension include changes in hemostasis and coagulation, ascites, pulmonary involvement, renal involvement, hepatic encephalopathy, and varices (Flow Diagram 4.2).

4.5.1 Hemostasis

Chronic liver disease leads to a form of "rebalanced" hemostasis. This is due to diminished hepatic function leading to both procoagulant and anticoagulant effects. All stages of the hemostatic process may be abnormal, including primary hemostasis (platelet adhesion and activation), coagulation (generation and cross-linking of fibrin), and fibrinolysis (clot dissolution). Risk of bleeding and thrombosis in an individual depends upon the balance or imbalance between altered blood flow, qualitative and quantitative dysfunction of platelets, and endothelial cell dysfunction [14, 15].

Coagulation factor defects Almost all of the coagulation factors (Factor I, II, V, VII, IX, X, and XI) except factor VIII (produced by endothelial cells) are produced by hepatocytes [16, 17]. Additionally, hepatocytes also help in post-translational modification (glycosylation, gamma-carboxylation) of certain factors, which is crucial for the activation of these factors. Chronic liver disease impairs both synthesis and post-translational modifications of clotting factors affecting coagulation in cirrhosis. In some liver disease (alcoholics), deficiency of vitamin K further exacerbates the deficiency and modification of vitamin K dependent factors (factor II, VII, IX, and X) [18, 19]. Qualitative defects in fibrinogen also contribute to the coagulopathy of cirrhosis.

Thrombocytopenia and platelet dysfunction Patients with cirrhosis have both qualitative and quantitative defects in platelet functions. The correlation between platelet count and clinical bleeding is weak [20]. Thrombocytopenia in liver diseases has multiple mechanisms, which includes impaired platelet production (due to decreased hepatic synthesis of thrombopoietin), bone marrow suppression (alcohol use, HCV infection, drugs), and sequestration platelets in the spleen due to portal hypertension induced hypersplenism. Also, coexisting uremia,



Flow Diagram 4.2 Complications of cirrhosis and portal hypertension

infection, and endotoxemia of sepsis contribute to thrombocytopenia.

Altered fibrinolytic system The fibrinolytic system is altered in patients with cirrhosis. Often fibrinolysis (dissolution of fibrin clot) is increased in chronic liver disease; however clinically significant hyperfibrinolysis is less commonly found in decompensated cirrhosis [21]. Hyperfibrinolysis promotes premature clot dissolution and interferes with clot formation due to the consumption of clotting factors. Hyperfibrinolysis in cirrhosis is associated with multiple mechanisms, which include: increased levels of tissue plasminogen activator (tPA) (which generates plasmin), decreased levels of alpha 2 antiplasmin, factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI) [22–24].

Prothrombotic changes The liver is the primary producer of endogenous inhibitors of coagulation (e.g., protein S, protein C, antithrombin) and fibrinolytic factors. Reduced level of these natural inhibitors in cirrhosis is responsible for the prothrombotic state [25, 26]. Also, elevated levels of Von Willebrand factor (VWF) and certain acute phase reactants (plasminogen activator inhibitor 1 (PAI-1)) may contribute to prothrombotic state [27, 28]. Reduced vascular flow also contributes to local prothrombotic tendencies.

Hemostatic abnormalities in chronic liver disease are similar regardless of the underlying cause. However, some differences have been noted, such as cholestatic liver diseases [primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)] appear to have a less pronounced effect on anticoagulant than procoagulant mechanisms and may be at higher risk for portal vein thrombosis. Nonalcoholic fatty liver disease (NAFLD) may confer a greater prothrombotic risk whereas acute-on-chronic liver failure (ACLF) may present with unique coagulopathies.

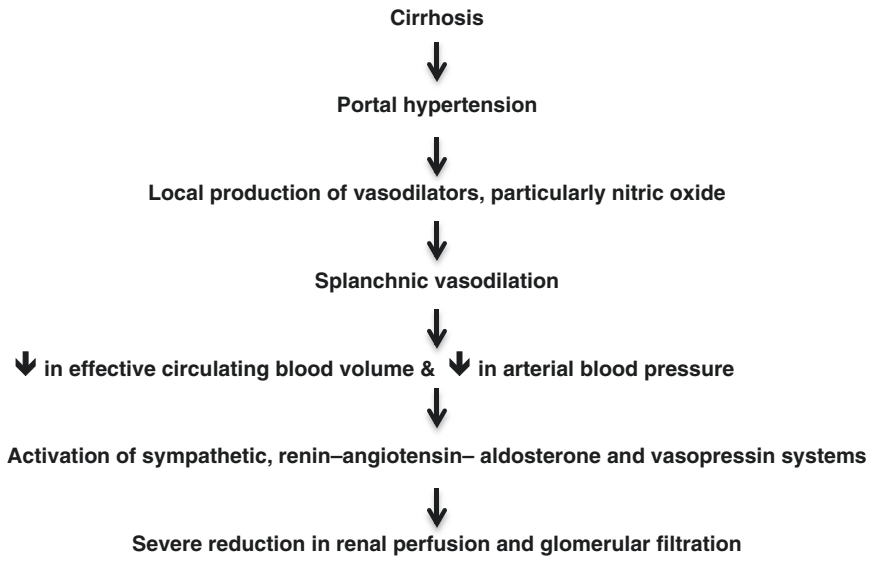
4.5.2 Cardiac Manifestations

Hyperdynamic circulation is the hallmark of cirrhosis which is characterized by a high cardiac output, low arterial blood pressure, and low systemic vascular resistance. Although these patients have an increased intravascular volume, most of this volume is sequestrated in the dilated and collateralized splanchnic circulation. Thus the effective circulating volume is reduced. The root cause of these changes is the portal hypertension, which is responsible for production of many vasodilators (natriuretic peptides, vasoactive intestinal peptide, endotoxin, glucagon) especially nitric oxide [29, 30]. Furthermore excessive production of vasodilators also leads to diminished circulatory responsivity to sympathetic stimulation.

Individuals with cirrhosis often have combinations of other cardiac abnormalities apart from hyperdynamic circulation which is termed as "cirrhotic cardiomyopathy" [1]. The four key components of this are (1) increase in cardiac output and decrease in systemic vascular resistance, (2) systolic and diastolic dysfunction, (3) reduced cardiac responsiveness to adrenergic stimulation, and (4) electrophysiologic abnormalities. The severity of cardiac dysfunction is directly correlated with the severity of liver disease.

4.5.3 Renal Dysfunction

Renal dysfunction is an important factor in the prediction of mortality and prognosis in cirrhosis. Renal dysfunction in cirrhosis is mainly caused by inappropriate retention of sodium and free water, together with renal hypoperfusion, which leads to a decrease in glomerular filtration rate (GFR) [31–33]. The hepatorenal syndrome (HRS) is one of the extreme manifestations of the renal response to the circulatory abnormalities of advanced cirrhosis. HRS is a diagnosis of exclu-



Flow Diagram 4.3 Pathophysiology of HRS

sion and is associated with a poor prognosis [32, 33]. The pathophysiology of HRS is shown in Flow Diagram 4.3.

Arterial vasodilatation in the splanchnic circulation, triggered by excessive production of nitric oxide (vasodilator), plays a central role in the hemodynamic changes and decline in renal function and perfusion. Elevated levels of renal prostaglandins help in maintaining renal perfusion.

Although HRS is the most common differential diagnosis of acute renal dysfunction in cirrhotic, it only accounts for 23% of the cases of acute kidney injury in hospitalized cirrhotic patients. Thus, cirrhotic patients are also at high risk of other causes of renal dysfunction, such as parenchymal renal disease, sepsis, nephrotoxicity, and hypovolemia. In addition possibilities of co-existence of other comorbidities (glomerulonephritis, diabetic nephropathy, immunonephropathies associated with hepatitis C, amyloidosis, SLE, etc.) should be kept in mind. Individuals with cirrhosis are also at high risk for hypovolemia from other causes like gastrointestinal bleeding, use of diuretic and diarrhea resulting from lactulose or rifaximin administration.

HRS is classified into two types (Type 1 and Type 2) as per its presentation; however the mechanism and pathophysiology remain the same in both the types (Table 4.2).

Table 4.2 Classification of HRS

Type-1 HRS	Type-2 HRS
• Rapidly progressive renal failure, typically represented by at least a doubling of serum creatinine over the course of 2 weeks	• Renal impairment that is less severe than that observed with type 1 disease
• More serious, median survival of 2–4 weeks without therapy	• Median survival is about 6 months
• Associated with failure of other organ system	• Presents with ascites that is resistant to diuretics

4.5.4 Pulmonary Complications

No risk factor other than presence of portal hypertension is associated with the presence of pulmonary complications in chronic liver disease and cirrhosis. The presence of vascular abnormalities in the setting of portal hypertension is the hallmark of pulmonary complications in cir-

rhosis [34, 35]. Two distinct types of vascular abnormalities have been recognized which affect the morbidity and mortality. These are named as hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN). When these pulmonary complications are present in a patient, they overshadow the symptoms of liver disease.

HPS is defined by a triad of liver dysfunction, unexplained hypoxemia, and intrapulmonary vascular dilatation (IPVD). The diagnostic criteria are mentioned in Table 4.3.

Table 4.3 Diagnostic criteria for HPS

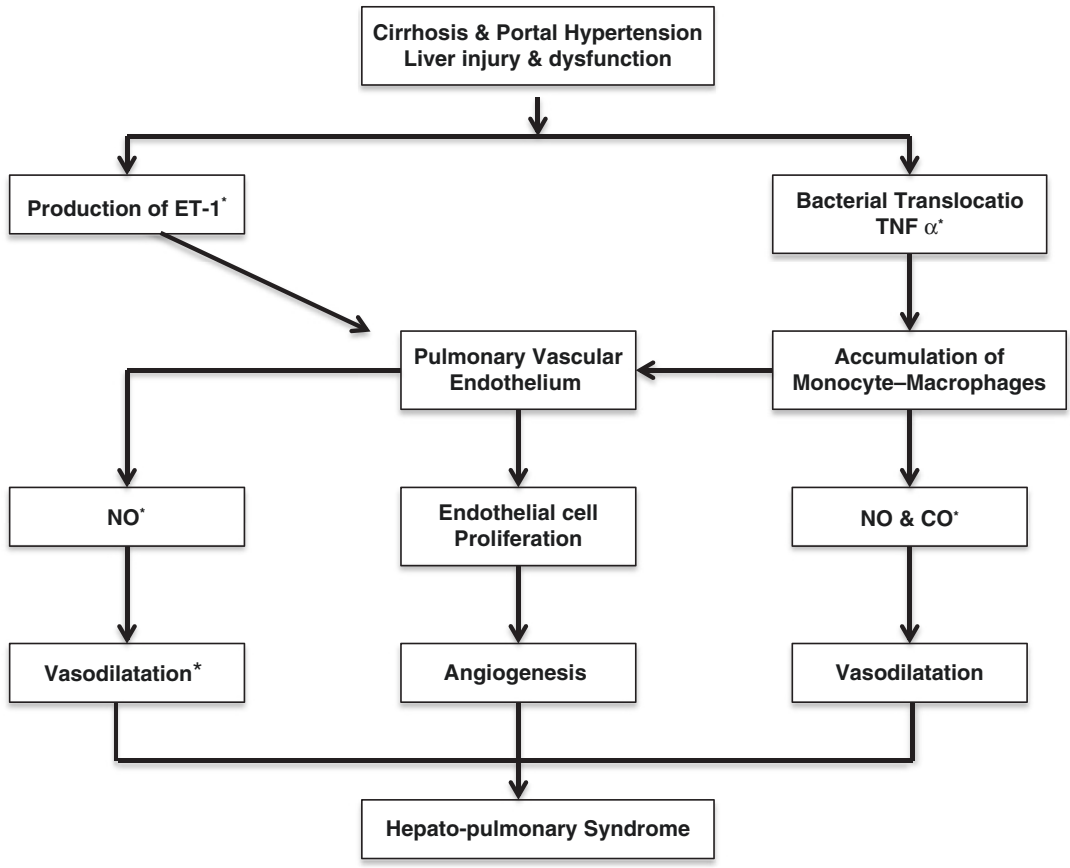
1. **Liver dysfunction**: Presence of portal hypertension
2. **Hypoxemia**: Room air partial pressure of oxygen (PO_2) <80 mmHg or alveolar–arterial oxygen gradient ($P_AO_2 - PaO_2$) ≥15 mmHg
3. **Pulmonary vascular dilatation**: Positive contrast echocardiography

The pathogenesis of HPS is not clearly defined. However various factors have been implicated as per different experimental studies [36–39]. The pathogenesis is shown in the Flow Diagram 4.4.

Pulmonary capillary dilation and less commonly direct arteriovenous connections are the pathogenic process of HPS, regardless of the mechanism. The resulting IPVDs are associated with HPS-related hypoxemia via ventilation-perfusion mismatch and oxygen diffusion limitation and rarely via shunt [35, 37].

PPHTN is defined as pulmonary hypertension that exists in a patient who has portal hypertension with no other known cause. The diagnostic criteria for PPHTN are mentioned in Table 4.4.

PPHTN occurs only in 2% of individuals with portal hypertension [1]. PPHTN is not related to the severity of the underlying liver disease or por-



Flow Diagram 4.4 Pathogenesis of HPS. *ET 1* endothelin 1, *TNF α* tissue necrosis factor, *NO* nitric oxide, *CO* carbon monoxide

Table 4.4 Diagnostic criteria for PPHTN

1.	Clinical evidence of portal hypertension
2.	Mean pulmonary artery pressure (PAP) >25 mmHg at rest or >30 mmHg during exercise
3.	Mean pulmonary artery occlusion pressure (PAOP) <15 mmHg
4.	Pulmonary vascular resistance (PVR) >240 dynes/s/cm^5

tal hypertension. Female patients, autoimmune hepatitis, and chronic hepatitis C are the risk factors for the development of PPHTN.

Vascular proliferation as a reaction to the shear stress of chronically elevated cardiac output has been described as the most common theory regarding the pathophysiology of PPHTN. However increased association with female gender and autoimmune hepatitis suggest humoral and immunogenic mechanisms. Also, increased level of endothelin has been associated with PPHTN.

4.5.5 Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a spectrum of potentially reversible neuropsychiatric abnormalities that can be associated with both acute and chronic liver failure. The manifestations varies from subclinical abnormalities to gross neurologic and behavioral derangements. The exact mechanism of brain dysfunction is still not known. However, it is not a single clinical entity and may be manifested as a result of a reversible metabolic encephalopathy, brain atrophy, brain edema, or any combination of these conditions.

HE is often associated with features of advanced and end-stage liver disease like ascites, hypoalbuminemia, hyperbilirubinemia, and coagulopathy. Failure of the diseased liver to adequately metabolize certain substances leads to accumulation of these neurotoxic substances responsible for neuropsychiatric abnormalities. Among the metabolic factors, ammonia is most commonly implicated; however there may be a role of inhibitory neurotransmission through gamma-aminobutyric acid (GABA) receptors in the central nervous system and changes in central neurotransmitters and circulating amino acids [40].

4.5.5.1 Ammonia Hypothesis

The pathophysiology of how ammonia causes encephalopathy is illustrated in Flow Diagram 4.5.

Elevated levels of glutamate are responsible for the neuroexcitatory signs of HE whereas the neuroinhibitory state is due to the downregulation of glutamate receptors and inactivation of astrocyte glutamate transporters [40–42].

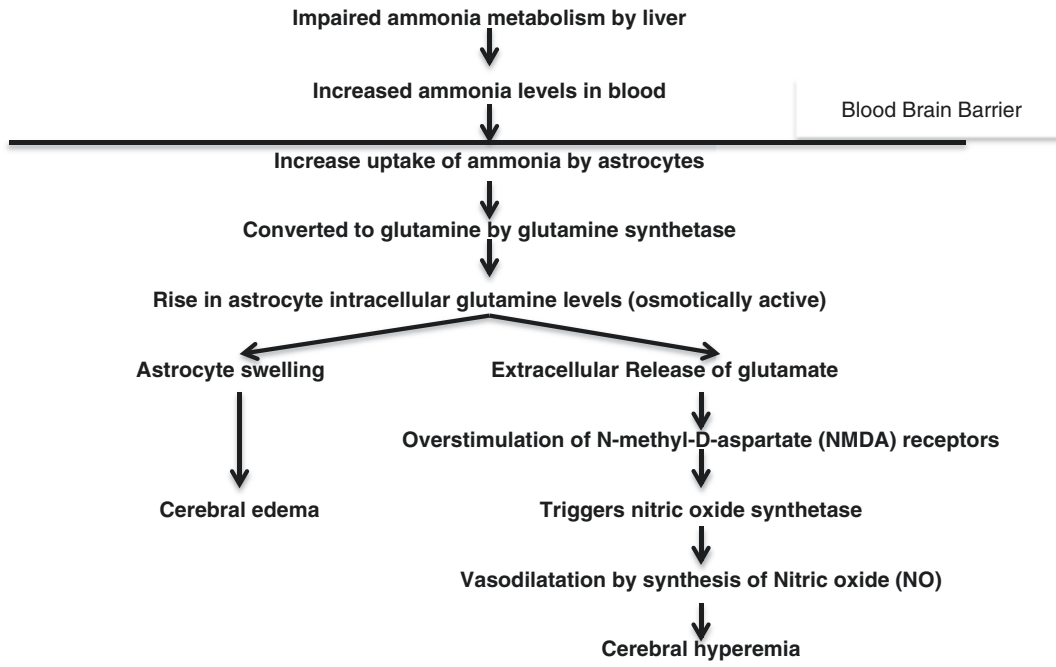
Although historically hyperammonemia has been attributed as the main cause of HE, severity of HE does not correlate with ammonia levels. Thus several other hypotheses are used to explain the mechanism of HE.

4.5.5.2 Impaired Neurotransmission Hypothesis

Increased tone of the inhibitory gamma-aminobutyric acid (GABA)A-benzodiazepine neurotransmitter system has been implicated in the development of HE; however contributing evidence are lacking to prove this hypothesis [43, 44]. Other endogenous GABA receptor agonists, oxidative stress, inflammatory mediators, and abnormal serotonin and histamine neurotransmission have been proposed to have a role in the pathogenesis of HE, but lack significant evidence.

4.5.6 Ascites

Ascites (defined as the pathologic accumulation of fluid in the peritoneal cavity) is the most common complication of cirrhosis. Portal hypertension is essential for the development of ascites. A portal pressure of >12 mmHg has been implicated in the pathogenesis of ascites. Various anatomical, biochemical, and pathophysiological abnormalities are responsible for the development of ascites in cirrhosis. Previously, underfill theory and overfill theory were popular for understanding the mechanism of ascites [45, 46]. However nowadays the arterial dilatation theory



Flow Diagram 4.5 Pathogenesis of HE

is most popular and accepted theory explaining the formation of ascites [47, 48]. The various factors responsible for ascites in cirrhosis are mentioned in Table 4.5.

Table 4.5 Factors responsible for ascites

Circulatory factors	Vascular factors
• Reduced SVR	• Splanchnic vasodilatation
• Reduced arterial pressure	• Pulmonary vasodilatation
• Increased heart rate	
• Increased plasma volume	
• Reduced renal blood flow	
Functional factors	Biochemical factors
• Activation of systemic and renal vasodilator	• Sodium retention
• Activation of systemic vasoconstrictor	• Water retention
• Reduction in GFR	• Increased systemic nitric oxide
	• Increased systemic prostaglandin
	• Increased renal nitric oxide and prostaglandins

4.5.7 Varices

Varices, particularly esophageal varices, are one of the end results of portal hypertension. In cirrhosis, increases in portal pressure result from distorted hepatic architecture left in the wake of inflammatory insults. Fibrosis and regenerative nodules cause impedance to splanchnic flow through the liver and lead to the formation of portosystemic collaterals, particularly with the gastric and esophageal venous systems [49–51]. Rupture of the high-pressure collaterals that are formed is a highly lethal and feared complication of portal hypertension.

Chronic liver disease may be caused by varied etiologies but persistent or recurrent insult leading to inflammation remains the core stone of pathophysiology. Cirrhosis represents the last stage of this inflammation, where progressive hepatic fibrosis causes distortion of the hepatic architecture and the formation of regenerative nodules. Initially these changes may be revers-

ible; however it is irreversible in its advanced stages. Patients with cirrhosis are susceptible to a variety of complications due to the anatomical and physiological changes in the liver. The prognosis of cirrhosis is highly variable since it is influenced by a number of factors, including etiology, severity, presence of complications, and comorbid diseases.

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