**CIRRHOSIS**

Cirrhosis represents the final common histologic pathway for a wide variety of chronic liver diseases. The term cirrhosis was first introduced by Laennec in 1826. It is derived from the Greek term scirrhus and is used to describe the orange or tawny surface of the liver seen at autopsy.

Many forms of liver injury are marked by fibrosis. Fibrosis is defined as an excess deposition of the components of extracellular matrix (ie, collagens, glycoproteins, proteoglycans) within the liver. This response to liver injury potentially is reversible. In contrast, cirrhosis is not a reversible process.

Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over weeks to years. Indeed, patients with hepatitis C may have chronic hepatitis for as long as 40 years before progressing to cirrhosis.

Often a poor correlation exists between histologic findings and the clinical picture. Some patients with cirrhosis are completely asymptomatic and have a reasonably normal life expectancy. Other individuals have a multitude of the most severe symptoms of end-stage liver disease and have a limited chance for survival. Common signs and symptoms may stem from decreased hepatic synthetic function (eg, coagulopathy), decreased detoxification capabilities of the liver (eg, hepatic encephalopathy), or portal hypertension (eg, variceal bleeding).

**Epidemiology**

Chronic liver disease and cirrhosis result in 26,000-35,000 deaths each year in the United States. Cirrhosis is the ninth leading cause of death in the United States and is responsible for 1.2% of all US deaths. Many patients die from the disease in their fifth or sixth decade of life. Each year, 2000 additional deaths are attributed to fulminant hepatic failure (FHF). FHF may be caused viral hepatitis (eg, hepatitis A and B), drugs (eg, acetaminophen), toxins (eg, Amanita phalloides, the yellow death-cap mushroom), autoimmune hepatitis, Wilson disease, and a variety of less common etiologies. Cryptogenic causes are responsible for one third of fulminant cases. Patients with the syndrome of FHF have a 50-80% mortality rate unless they are salvaged by liver transplantation.

**Etiology**

Causes of cirrhosis

* Hepatitis C (26%)
* Alcoholic liver disease (21%)
* Hepatitis C plus alcoholic liver disease (15%)
* Cryptogenic causes (18%)
* Hepatitis B, which may be coincident with hepatitis D (15%)
* Autoimmune hepatitis
* Primary biliary cirrhosis
* Secondary biliary cirrhosis (associated with chronic extrahepatic bile duct obstruction)
* Primary sclerosing cholangitis
* Hemochromatosis
* Wilson disease
* Alpha-1 antitrypsin deficiency

**Pathophysiology of hepatic fibrosis**

The development of hepatic fibrosis reflects an alteration in the normally balanced processes of extracellular matrix production and degradation. Extracellular matrix, the normal scaffolding for hepatocytes, is composed of collagens (especially types I, III, and V), glycoproteins, and proteoglycans. Stellate cells, located in the perisinusoidal space, are essential for the production of extracellular matrix. Stellate cells, which were once known as Ito cells, lipocytes, or perisinusoidal cells, may become activated into collagen-forming cells by a variety of paracrine factors. Such factors may be released by hepatocytes, Kupffer cells, and sinusoidal endothelium following liver injury. As an example, increased levels of the cytokine transforming growth factor beta1 (TGF-beta1) are observed in patients with chronic hepatitis C and those with cirrhosis. TGF-beta1, in turn, stimulates activated stellate cells to produce type I collagen.

Increased collagen deposition in the space of Disse (the space between hepatocytes and sinusoids) and the diminution of the size of endothelial fenestrae lead to the capillarization of sinusoids. Activated stellate cells also have contractile properties. Both capillarization and constriction of sinusoids by stellate cells contribute to the development of portal hypertension.

Future drug strategies to prevent fibrosis may focus on reducing hepatic inflammation, inhibiting stellate cell activation, inhibiting the fibrogenic activities of stellate cells, and stimulating matrix degradation.

**Main manifistetion of cirrhosis**

**PORTAL HYPERTENSION**

Causes

The normal liver has the ability to accommodate large changes in portal blood flow without appreciable alterations in portal pressure. Portal hypertension results from a combination of increased portal venous inflow and increased resistance to portal blood flow. Patients with cirrhosis demonstrate increased splanchnic arterial flow and, accordingly, increased splanchnic venous inflow into the liver. Increased splanchnic arterial flow is explained partly by decreased peripheral vascular resistance and increased cardiac output in the patient with cirrhosis. Nitric oxide appears to be one of the major driving forces for this phenomenon. Furthermore, evidence for splanchnic vasodilation exists. Putative splanchnic vasodilators include glucagon, vasoactive intestinal peptide, substance P, prostacyclin, bile acids, tumor necrosis factor-alpha (TNF-alpha), and nitric oxide.

Clinically, increased resistance across the sinusoidal vascular bed of the liver may be a more important factor in the development of portal hypertension. Factors that increase resistance to blood flow include disruption of hepatic architecture and compression of hepatic venules by regenerating nodules, increased collagen deposition in the space of Disse, and increased intrahepatic levels of locally acting vasoconstricting chemicals. As an example, endothelin, which is produced by hepatocytes, may bind to receptors on stellate cells. This, in turn, may lead to stellate cell contraction and vasoconstriction of the hepatic sinusoid.

Intrahepatic causes of portal hypertension are divided into

1. presinusoidal,

2. sinusoidal,

3. postsinusoidal conditions.

1. The classic form of presinusoidal disease is caused by the deposition of Schistosoma oocytes in presinusoidal portal venules, with the subsequent development of granulomata and portal fibrosis. Schistosomiasis is the most common noncirrhotic cause of variceal bleeding worldwide. Schistosoma mansoni infection is described in Puerto Rico, Central and South America, the Middle East, and Africa. Schistosoma japonicum is described in the Far East. Schistosoma hematobium, observed in the Middle East and Africa, can produce portal fibrosis but more commonly is associated with urinary tract deposition of eggs.

2. The classic sinusoidal cause of portal hypertension is cirrhosis.

3. The classic postsinusoidal condition is an entity known as venoocclusive disease. Obliteration of the terminal hepatic venules may result from ingestion of pyrrolizidine alkaloids in Comfrey tea or Jamaican bush tea and following the high-dose chemotherapy that precedes bone marrow transplantation.

Posthepatic causes of portal hypertension may include chronic right-sided heart failure and tricuspid regurgitation and obstructing lesions of the hepatic veins and inferior vena cava.

**ASCITES**

Ascites is defined as an accumulation of excessive fluid within the peritoneal cavity and may be a complication of both hepatic and nonhepatic diseases.

The 4 most common causes of ascites in North America and Europe are cirrhosis, neoplasm, congestive heart failure, and tuberculous peritonitis.

In the past, ascites was classified as being a transudate or an exudate. In transudative ascites, fluid was said to cross the liver capsule because of an imbalance in Starling forces. In general, ascites protein was less than 2.5 g/dL. Classic causes of transudative ascites are portal hypertension secondary to cirrhosis and congestive heart failure.

In exudative ascites, fluid was said to weep from an inflamed or tumor-laden peritoneum. In general, ascites protein was greater than 2.5 g/dL. Examples included peritoneal carcinomatosis and tuberculous peritonitis.

**The role of portal hypertension in the pathogenesis of cirrhotic ascites**

The formation of ascites in cirrhosis depends on the presence of unfavorable Starling forces within the hepatic sinusoid and on some degree of renal dysfunction. Patients with cirrhosis are observed to have increased hepatic lymphatic flow.

Fluid and plasma proteins diffuse freely across the highly permeable sinusoidal endothelium into the space of Disse. Fluid in the space of Disse, in turn, enters the lymphatic channels that run within the portal and central venous areas of the liver.

Because the transsinusoidal oncotic gradient is approximately zero, the increased sinusoidal pressure that develops in portal hypertension increases the amount of fluid entering the space of Disse. When the increased hepatic lymph production observed in portal hypertension exceeds the ability of the cisterna chyli and thoracic duct to clear the lymph, fluid crosses into the liver interstitium. Fluid may then extravasate across the liver capsule into the peritoneal cavity.

**The role of renal dysfunction in the pathogenesis of cirrhotic ascites**

Patients with cirrhosis experience sodium retention, impaired free water excretion, and intravascular volume overload. These abnormalities may occur even in the setting of a normal glomerular filtration rate. To some extent, these abnormalities are due to increased levels of renin and aldosterone. Why the renin-angiotensin-aldosterone system is stimulated in cirrhosis remains unknown.

The underfill hypothesis postulates that the formation of ascites leads to decreased effective intravascular volume and to stimulation of the renin-angiotensin system. The hypothesis is supported by the fact that head-out-of-water immersion of the patient with cirrhosis results in plasma redistribution and a decrease in renin, aldosterone, antidiuretic hormone, and norepinephrine levels. The hypothesis is contradicted by the presence of increased intravascular volume in patients with cirrhosis.

The overflow hypothesis states that in cirrhosis, intrahepatic mechanoreceptors sense decreased hepatocyte perfusion with portal blood. This event stimulates sodium and water retention. A subsequent increase in plasma volume then results in an overflow of fluid into the peritoneal cavity.

The peripheral arterial vasodilation hypothesis states that splanchnic arterial vasodilation, perhaps driven by nitric oxide and glucagon, leads to intravascular underfilling. This leads to stimulation of the renin-angiotensin system, the sympathetic nervous system, and antidiuretic hormone release. This is followed by an increase in sodium and water retention, an increase in plasma volume, and the overflow of fluid into the peritoneal cavity.

**Clinical features of ascites**

Ascites is suggested by the presence of a number of findings upon physical examination, which are abdominal distention, bulging flanks, shifting dullness, and elicitation of a "puddle sign" in patients in the knee-elbow position. A fluid wave may be elicited in patients with massive tense ascites. However, physical examination findings are much less sensitive than performing abdominal ultrasonography, which can detect as little as 30 mL of fluid. Furthermore, ultrasound with Doppler can help assess the patency of hepatic vessels. Factors associated with worsening of ascites include excess fluid or salt intake, malignancy, venous occlusion (eg, Budd-Chiari syndrome), progressive liver disease, and spontaneous bacterial peritonitis (SBP).

Patients with massive ascites may experience abdominal discomfort, depressed appetite, and decreased oral intake. Diaphragmatic elevation may lead to symptoms of dyspnea. Pleural effusions may result from the passage of ascitic fluid across channels in the diaphragm.

Umbilical and inguinal hernias are common in patients with moderate and massive ascites. The use of an elastic abdominal binder may protect the skin overlying a protruding umbilical hernia from maceration and may help prevent rupture and subsequent infection. Timely large-volume paracentesis also may help to prevent this disastrous complication. Umbilical hernias should not undergo elective repair unless patients are significantly symptomatic or their hernias are irreducible. As with all other surgeries in patients with cirrhosis, herniorrhaphy carries multiple potential risks such as intraoperative bleeding, postoperative infection, and liver failure because of anesthesia-induced reductions in hepatic blood flow. However, these risks become acceptable in patients with severe symptoms from their hernia. Urgent surgery is necessary in the patient whose hernia has been complicated by bowel incarceration.

**Paracentesis in the diagnosis of ascites**

Paracentesis is essential in determining whether ascites is caused by portal hypertension or by another process. Ascites studies also are used to rule out infection and malignancy. Paracentesis should be performed in all patients with either new onset of ascites or worsening ascites.

**Medical treatment of ascites**

Therapy for ascites should be tailored to the patient's needs. Some patients with mild ascites respond to sodium restriction or diuretics taken once or twice per week. Other patients require aggressive diuretic therapy, careful monitoring of electrolytes, and occasional hospitalization to facilitate even more intensive diuresis.

* **Sodium restriction**

Salt restriction is the first line of therapy. In general, patients begin with a diet containing less than 2000 mg sodium per day. Some patients with refractory ascites require a diet containing less than 500 mg sodium per day. However, ensuring that patients do not construct diets that might place them at risk for calorie and protein malnutrition is important. Indeed, the benefit of commercially available liquid nutritional supplements (which often contain moderate amounts of sodium) often exceeds the risk of slightly increasing the patient's salt intake.

* **Diuretics**

Diuretics should be considered the second line of therapy.

1. Spironolactone (Aldactone) blocks the aldosterone receptor at the distal tubule. It is dosed at 50-300 mg once per day. Although the drug has a relatively short half-life, its blockade of the aldosterone receptor lasts for at least 24 hours. Adverse effects of spironolactone include hyperkalemia, gynecomastia, and lactation. Other potassium-sparing diuretics, including amiloride and triamterene, may be used as alternative agents, especially in patients complaining of gynecomastia.

2. Furosemide (Lasix) may be used as a solo agent or in combination with spironolactone. The drug blocks sodium reuptake in the loop of Henle. It is dosed at 40-240 mg per day in 1-2 divided doses. Patients infrequently need potassium repletion when furosemide is dosed in combination with spironolactone.

Aggressive diuretic therapy in hospitalized patients with massive ascites can safely induce a 0.5- to 1-kg weight loss per day, providing that patients undergo careful monitoring of renal function. The author's practice is to administer intravenous furosemide following intravenous infusion of albumin at 25 g twice per day, in addition to ongoing therapy with spironolactone. Diuretic therapy should be held in the event of electrolyte disturbances, azotemia, or the induction of hepatic encephalopathy.

* The ability of intravenous albumin to promote diuresis in some patients with cirrhosis and ascites is well known.

Albumin also may protect against the development of renal insufficiency. One recent report supports the use of intravenous albumin in patients with SBP. Patients receiving cefotaxime and albumin at 1 g/kg/day experienced a lower risk of renal failure and a lower in-hospital mortality rate than patients treated with cefotaxime and conventional fluid management.

* **Large-volume paracentesis**

Aggressive diuretic therapy is ineffective in controlling ascites in approximately 5-10% of patients. Such patients with massive ascites may need to undergo large-volume paracentesis in order to receive relief from symptoms of abdominal discomfort, anorexia, or dyspnea. The procedure also may help reduce the risk of umbilical hernia rupture.

Large-volume paracentesis was first used in ancient times. It fell out of favor from the 1950s through the 1980s with the advent of diuretic therapy and following a handful of case reports describing paracentesis-induced azotemia. In 1987, Gines and colleagues demonstrated that large-volume paracentesis could be performed with minimal or no impact on renal function. This and other studies showed that 5-15 L of ascites could be removed safely at one time. Large-volume paracentesis is thought to be safe in patients with peripheral edema and in patients not currently treated with diuretics. Debate exists whether colloid infusions (eg, with 5-10 g albumin per 1 L ascites removed) are necessary to prevent intravascular volume depletion in patients who are receiving ongoing diuretic therapy or in patients with mild or moderate underlying renal insufficiency.

**Peritoneovenous shunts**

LeVeen shunts and Denver shunts are devices that permit the return of ascites fluid and proteins to the intravascular space. Plastic tubing inserted subcutaneously under local anesthesia connects the peritoneal cavity to the internal jugular vein or subclavian vein via a pumping chamber. These devices are successful at relieving ascites and reversing protein loss in some patients. However, serious complications are observed in 10% of the recipients of these devices. Complications include peritoneal infection, sepsis, disseminated intravascular coagulation, and congestive heart failure. Shunts may clot and require replacement in an additional 30% of patients. However, peritoneovenous shunts may be a reasonable form of therapy for patients with refractory ascites who are not candidates for TIPS or liver transplantation.

**Portosystemic shunts and transjugular intrahepatic portosystemic shunts**

The prime indication for portocaval shunt surgery is the management of refractory variceal bleeding. However, since 1945, the medical field has recognized that portocaval shunts, by decompressing the hepatic sinusoid, may improve ascites. The performance of a side-to-side portocaval shunt for ascites management must be weighed against the approximate 5% mortality rate associated with this surgery and the chance (as high as 30%) of inducing hepatic encephalopathy.

TIPS is an effective tool in managing massive ascites in some patients. Ideally, TIPS placement produces a decrease in sinusoidal pressure and a decrease in plasma renin and aldosterone levels, with subsequent improved urinary sodium excretion. In one study, 74% of patients with refractory ascites achieved complete remission of ascites within 3 months of TIPS placement. However, patient selection for the procedure is important. Creation of a TIPS has the potential to worsen preexisting hepatic encephalopathy and exacerbate liver dysfunction in patients with severe underlying liver failure. In the author's opinion, TIPS use should be reserved for patients with Child class B cirrhosis or patients with Child class C cirrhosis without severe coagulopathy or encephalopathy. Furthermore, shunt stenosis is observed in half the cases within 1 year of placement, necessitating angiographic revision. Thus, patients must be willing to return to the hospital for Doppler and angiographic follow-up of TIPS patency.

**Liver transplantation**

Patients with massive ascites have a less than 50% 1-year survival rate. Liver transplantation should be considered as a potential means of salvaging the patient prior to the onset of intractable liver failure or hepatorenal syndrome.

**HEPATIC ENCEPHALOPATHY**

Hepatic encephalopathy is a syndrome observed in some patients with cirrhosis that is marked by personality changes, intellectual impairment, and a depressed level of consciousness. The diversion of portal blood into the systemic circulation appears to be a prerequisite for the syndrome. Indeed, hepatic encephalopathy may develop in patients who do not have cirrhosis who undergo portocaval shunt surgery.

**Pathogenesis**

A number of theories have been postulated to explain the pathogenesis of hepatic encephalopathy in patients with cirrhosis. Patients may have altered brain energy metabolism and increased permeability of the blood-brain barrier. The latter may facilitate the passage of neurotoxins into the brain. Putative neurotoxins include short-chain fatty acids, mercaptans, false neurotransmitters (eg, tyramine, octopamine, and beta-phenylethanolamines), ammonia, and gamma-aminobutyric acid (GABA).

* **The ammonia hypothesis**

Ammonia is produced in the GI tract by bacterial degradation of amines, amino acids, purines, and urea. Normally, ammonia is detoxified in the liver by conversion to urea and glutamine. In liver disease or portosystemic shunting, portal blood ammonia is not converted efficiently to urea. Increased levels of ammonia may enter the systemic circulation because of portosystemic shunting.

Ammonia has multiple neurotoxic effects, including altering the transit of amino acids, water, and electrolytes across the neuronal membrane. Ammonia also can inhibit the generation of both excitatory and inhibitory postsynaptic potentials. Therapeutic strategies to reduce serum ammonia levels tend to improve hepatic encephalopathy. However, approximately 10% of patients with significant encephalopathy have normal serum ammonia levels. Furthermore, many patients with cirrhosis have elevated ammonia levels without evidence of encephalopathy.

* **The gamma-aminobutyric acid hypothesis**

GABA is a neuroinhibitory substance produced in the GI tract. When GABA crosses the extrapermeable blood-brain barrier of a patient with cirrhosis, it interacts with supersensitive postsynaptic GABA receptors. The GABA receptor, in conjunction with receptors for benzodiazepines and barbiturates, regulates a chloride ionophore. Binding of GABA to its receptor permits an influx of chloride ions into the postsynaptic neuron, leading to the generation of an inhibitory postsynaptic potential. Administration of benzodiazepines and barbiturates to patients with cirrhosis increases GABA-ergic tone and predisposes patients to depressed consciousness. The GABA hypothesis is supported by the clinical observation that flumazenil (a benzodiazepine antagonist) transiently can reverse hepatic encephalopathy in patients with cirrhosis.

**Clinical features of hepatic encephalopathy**

The symptoms of hepatic encephalopathy may range from mild to severe and may be observed in as many as 70% of patients with cirrhosis. Symptoms are graded on the following scale:

**Grade 0** - Subclinical; normal mental status, but minimal changes in memory, concentration, intellectual function, coordination

**Grade 1** - Mild confusion, euphoria or depression, decreased attention, slowing of ability to perform mental tasks, irritability, disorder of sleep pattern (ie, inverted sleep cycle)

**Grade 2** - Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, intermittent disorientation (usually for time)

**Grade 3** - Somnolent but arousable, unable to perform mental tasks, disorientation to time and place, marked confusion, amnesia, occasional fits of rage, speech is present but incomprehensible

**Grade 4** - Coma, with or without response to painful stimuli

Patients with mild and moderate hepatic encephalopathy demonstrate decreased short-term memory and concentration on mental status testing. Findings upon physical examination include asterixis and fetor hepaticus.

**Laboratory abnormalities in hepatic encephalopathy**

An elevated arterial or free venous serum ammonia level is the classic laboratory abnormality reported in patients with hepatic encephalopathy. This finding may aid in the assignment of a correct diagnosis to a patient with cirrhosis who presents with altered mental status. However, serial ammonia measurements are inferior to clinical assessment in gauging improvement or deterioration in patients under therapy for hepatic encephalopathy. No utility exists for checking the ammonia level in a patient with cirrhosis who does not have hepatic encephalopathy.

Some patients with hepatic encephalopathy have the classic but nonspecific electroencephalogram (EEG) changes of high-amplitude low-frequency waves and triphasic waves. EEG may be helpful in the initial workup of a patient with cirrhosis and altered mental status when ruling out seizure activity may be necessary.

CT scan and MRI studies of the brain may be important in ruling out intracranial lesions when the diagnosis of hepatic encephalopathy is in question.

**Common precipitants of hepatic encephalopathy**

Some patients with a history of hepatic encephalopathy may have normal mental status when under medical therapy. Others have chronic memory impairment in spite of medical management. Both groups of patients are subject to episodes of worsened encephalopathy. Common precipitants of hyperammonemia and worsening mental status are diuretic therapy, renal failure, GI bleeding, infection, and constipation. Dietary protein overload is an infrequent cause of worsening encephalopathy. Medications, notably opiates, benzodiazepines, antidepressants, and antipsychotic agents, also may worsen encephalopathy symptoms.

**Treatment of hepatic encephalopathy**

1. **Lactulose** is helpful in patients with the acute onset of severe encephalopathy symptoms and in patients with milder, chronic symptoms. This nonabsorbable disaccharide stimulates the passage of ammonia from tissues into the gut lumen and inhibits intestinal ammonia production. Initial lactulose dosing is 30 mL orally once or twice daily. Dosing is increased until the patient has 2-4 loose stools per day. Dosing should be reduced if the patient complains of diarrhea, abdominal cramping, or bloating. Higher doses of lactulose may be administered via either a nasogastric tube or rectal tube to hospitalized patients with severe encephalopathy. Other cathartics, including colonic lavage solutions that contain polyethylene glycol (PEG) (eg, Go-Lytely), also may be effective in patients with severe encephalopathy.

2. **Neomycin and other antibiotics** (eg, metronidazole, oral vancomycin, paromomycin, oral quinolones) serve as second-line agents. They work by decreasing the colonic concentration of ammoniagenic bacteria. Neomycin dosing is 250-1000 mg orally 2-4 times daily.

Other chemicals capable of decreasing blood ammonia levels are L-ornithine L-aspartate (available in Europe) and sodium benzoate.

3. **Low-protein diets** were recommended routinely in the past for patients with cirrhosis. High levels of aromatic amino acids contained in animal proteins were believed to lead to increased blood levels of the false neurotransmitters tyramine and octopamine, with resulting worsening of encephalopathy symptoms. In this author's experience, the vast majority of patients can tolerate a protein-rich diet (>1.2 g/kg/d) including well-cooked chicken, fish, vegetable protein, and, if needed, protein supplements. Although protein restriction may play a role in the management of the patient with an acute flare of hepatic encephalopathy, it rarely is necessary in patients with chronic encephalopathy symptoms. Furthermore, many patients with cirrhosis have protein-calorie malnutrition at baseline. The routine restriction of dietary protein intake increases their risk for worsening malnutrition.

**Other manifestations of cirrhosis; assessment of severity of cirrhosis**

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

As an example, patients with end-stage liver disease caused by hepatitis C might develop profound muscle wasting, marked ascites, and severe hepatic encephalopathy, with only mild jaundice.

In contrast, patients with end-stage primary biliary cirrhosis might be deeply icteric, with no evidence of muscle wasting. These patients may complain of extreme fatigue and pruritus and have no complications of portal hypertension.

In both cases, medical management is focused on the relief of symptoms. Liver transplantation should be considered as a potential therapeutic option, given the inexorable course of most cases of end-stage liver disease.

1. Many patients with cirrhosis experience fatigue, anorexia, weight loss, and muscle wasting.

2. Cutaneous manifestations of cirrhosis include jaundice, spider angiomata, skin telangiectasias (termed “paper money skin” by Dame Sheila Sherlock), palmar erythema, white nails, disappearance of lunulae, and finger clubbing, especially in the setting of hepatopulmonary syndrome.

3. Patients with cirrhosis may experience increased conversion of androgenic steroids into estrogens in skin, adipose tissue, muscle, and bone.

Males may develop gynecomastia and impotence. Loss of axillary and pubic hair is noted in both men and women. Hyperestrogenemia also may explain spider angiomata and palmar erythema.

4. Hematologic manifestations

Anemia may result from folate deficiency, hemolysis, or hypersplenism. Thrombocytopenia usually is secondary to hypersplenism and decreased levels of thrombopoietin. Coagulopathy results from decreased hepatic production of coagulation factors. If cholestasis is present, decreased micelle entry into the small intestine leads to decreased vitamin K absorption, with resulting reduction in hepatic production of factors II, VII, IX, and X. Patients with cirrhosis also may experience fibrinolysis and disseminated intravascular coagulation.

5. Pulmonary and cardiac manifestations

Patients with cirrhosis may have impaired pulmonary function. Pleural effusions and the diaphragmatic elevation caused by massive ascites may alter ventilation-perfusion relations. Interstitial edema or dilated precapillary pulmonary vessels may reduce pulmonary diffusing capacity.

**Assessment of the severity of cirrhosis**

The most common tool for gauging prognosis in cirrhosis is the Child-Turcotte-Pugh (CTP) system. Child and Turcotte first introduced their scoring system in 1964 as a means of predicting the operative mortality associated with portocaval shunt surgery. Pugh's revised system in 1973 substituted albumin for the less specific variable of nutritional status. More recent revisions use International Normalized Ratio (INR) in addition to prothrombin time.

Recent epidemiologic work shows that the CTP score may predict life expectancy in patients with advanced cirrhosis. A CTP score of 10 or greater is associated with a 50% chance of death within 1 year.

**TREATMENT OF CIRRHOSIS**

Specific medical therapies may be applied to many liver diseases in an effort to diminish symptoms and prevent or forestall the development of cirrhosis. Examples include prednisone and azathioprine for autoimmune hepatitis, interferon and other antiviral agents for hepatitis B and C, phlebotomy for hemochromatosis, ursodeoxycholic acid for primary biliary cirrhosis, and zinc and penicillamine for Wilson disease. These therapies become progressively less effective if chronic liver disease evolves into cirrhosis. Once cirrhosis develops, treatment is aimed at the management of complications as they arise. Certainly variceal bleeding, ascites, and hepatic encephalopathy are among the most serious complications experienced by patients with cirrhosis. However, attention also must be paid to patients' chronic constitutional complaints.

**Nutrition**

Many patients complain of anorexia, which may be compounded by the direct compression of ascites on the GI tract. Care should be taken to assure that patients receive adequate calories and protein in their diets. Patients frequently benefit from the addition of commonly available liquid and powdered nutritional supplements to the diet. Only rarely can patients not tolerate proteins in the form of chicken, fish, vegetables, and nutritional supplements. Institution of a low-protein diet in the fear that hepatic encephalopathy might develop places the patient at risk for the development of profound muscle wasting.

**Adjunctive therapies**

Zinc deficiency commonly is observed in patients with cirrhosis. Treatment with zinc sulfate at 220 mg orally twice daily may improve dysgeusia and can stimulate appetite. Furthermore, zinc is effective in the treatment of muscle cramps and is adjunctive therapy for hepatic encephalopathy.

**Pruritus** is a common complaint in both cholestatic liver diseases (eg, primary biliary cirrhosis) and in noncholestatic chronic liver diseases (eg, hepatitis C). Although increased serum bile acid levels once were thought to be the cause of pruritus, endogenous opioids are more likely to be the culprit pruritogens. Mild itching complaints may respond to treatment with antihistamines.

Cholestyramine is the mainstay of therapy for the pruritus of liver disease. Care should be taken to avoid coadministration of this organic anion binder with any other medication, to avoid compromising GI absorption. Other medications that may provide relief against pruritus include ursodeoxycholic acid, naltrexone (an opioid antagonist), rifampin, and ondansetron.

Patients with cirrhosis may develop osteoporosis. Supplementation with calcium and vitamin D is important in patients at high risk for osteoporosis, especially patients with chronic cholestasis, patients with primary biliary cirrhosis, and patients receiving corticosteroids for autoimmune hepatitis. The discovery of decreased bone mineralization upon bone densitometry studies also may prompt institution of therapy with an aminobisphosphonate (eg, alendronate sodium).

**Surgery in the patient with cirrhosis**

Surgery and general anesthesia carry increased risks in the patient with cirrhosis. Anesthesia reduces cardiac output, induces splanchnic vasodilation, and causes a 30- to 50%-reduction in hepatic blood flow. This places the cirrhotic liver at additional risk for decompensation. Surgery is said to be safe in the setting of mild chronic hepatitis. Its risk in patients with severe chronic hepatitis is unknown. Patients with well-compensated cirrhosis have an increased but acceptable risk of morbidity and mortality. A study of nonshunt abdominal surgeries demonstrated a 10% mortality rate for patients with Child class A cirrhosis as opposed to a 30% mortality rate for patients with Child class B cirrhosis and a 75% mortality rate for patients with Child class C cirrhosis. Thus, unless absolutely necessary, surgery should be avoided in the patient with cirrhosis. Although cholecystectomy was among the riskier surgeries noted, several recent reports have described the successful performance of laparoscopiccholecystectomy in patients with Child class A and B cirrhosis.

**Monitoring the patient with cirrhosis**

Patients with cirrhosis should undergo routine follow-up monitoring of their complete blood count, renal and liver chemistries, and prothrombin time. The author's policy is to monitor stable patients 3-4 times per year. The author performs routine diagnostic endoscopy to determine whether the patient has asymptomatic esophageal varices. Follow-up endoscopy is performed in 2 years if varices are not present. If varices are present, treatment is initiated with a nonselective beta-blocker (eg, propranolol, nadolol), aiming for a 25% reduction in heart rate, and a long-acting nitrate medication (eg, isosorbide-5-mononitrate). Such therapy offers effective primary prophylaxis against the new onset of variceal bleeding.

This author encourages the screening of patients to rule out the interval development of HCC. The author's practice is to perform abdominal ultrasonography and alpha-fetoprotein testing twice yearly, although the clinical utility and cost-effectiveness of this strategy remains controversial. Patients with suspected HCC should undergo ultrasound or liver biopsy guided by CT scan. If HCC is confirmed, the physician may elect to treat the patient with resection surgery, percutaneous injection therapy with ethanol or acetic acid, thermal ablation, or chemoembolization. Appropriate patients without evidence of extrahepatic disease, as determined by chest and abdominal CT scan and by bone scan, may require an accelerated course to liver transplantation.

**LIVER TRANSPLANTATION**

Liver transplantation has emerged as an important strategy in the management of patients with decompensated cirrhosis. Patients should be referred for consideration of liver transplantation after the first signs of hepatic decompensation, as marked by a score of 7 or greater using the CTP scoring system. The United Network for Organ Sharing states that this score is the minimum required to permit entry of a patient's name onto the national transplant waiting list. Other less common indications for liver transplantation include detection of HCC, recurrent biliary sepsis in the setting of primary sclerosing cholangitis, and hepatic osteodystrophy.

Contraindications for liver transplantation include severe cardiovascular or pulmonary disease, active drug or alcohol abuse, malignancy outside the liver, sepsis, or psychosocial problems that might jeopardize patients' abilities to follow their medical regimens after transplant. The presence of HIV in the bloodstream also is a contraindication to transplant. However, successful liver transplantations are now being performed in patients with no detectable HIV viral load due to antiretroviral therapy. Additional clinical study is required before liver transplantation can be offered routinely to such patients.

Advances in surgical technique, organ preservation, and immunosuppression have resulted in dramatic improvements in postoperative survival over the last 2 decades. In the early 1980s, the percentage of patients surviving 1 year and 5 years after liver transplant was only 70% and 15%, respectively. Now, patients can anticipate a 1-year survival rate of 85% and a 5-year survival rate of higher than 70%. Quality of life after liver transplant is good or excellent in most cases.

**HEPATIC FAILURE**

Acute liver failure (ALF) is a broad term that refers to both fulminant hepatic failure (FHF) and subfulminant hepatic failure (or late-onset hepatic failure). The latter term is reserved for patients with liver disease for up to 26 weeks prior to the development of hepatic encephalopathy. Some patients with previously unrecognized chronic liver disease decompensate and present with liver failure; although this technically is not FHF, discerning this at the time of presentation may not be possible (eg, Wilson disease).

FHF is a term used to describe the development of coagulopathy and encephalopathy as a result of acute hepatic decompensation within 8 weeks from the onset of illness. FHF may result from a variety of hepatic disease processes. Viral hepatitis and hepatotoxic drugs are the most common causes of FHF. Treatment of the underlying process is essential, but the common factor underlying the severity of illness is loss of hepatic function.

**Frequency**

Incidence of FHF appears to be low, with approximately 2000 cases annually occurring in the United States.

Acetaminophen or paracetamol overdoses are prominent causes of FHF in Europe and, in particular, Great Britain. In the developing world, acute hepatitis B virus (HBV) infection dominates as a cause of FHF because of the high prevalence of HBV. Hepatitis delta virus (HDV) superinfection is much more common in developing countries than in the United States because of the high rate of chronic HBV infection. Hepatitis E virus (HEV) is associated with a high incidence of FHF in women who are pregnant and is of concern in pregnant patients living in or traveling through endemic areas. These regions include, but are not limited to, Mexico and Central America, India and the subcontinent, and the Middle East.

Several factors contribute to morbidity and mortality. The etiologic factor leading to hepatic failure and the development of complications is key. In general, the best prognoses occur in the absence of complications. Spontaneous bacterial peritonitis, adult respiratory distress syndrome, hepatorenal syndrome, bleeding, cerebral edema, and sepsis pose challenges that reduce the probability of survival.

Viral hepatitis: In patients with FHF due to hepatitis A virus (HAV), survival rates are greater than 50-60%. These patients account for a substantial proportion (10-20%) of the pediatric liver transplants in some countries despite the relatively mild infection that is observed in many children infected with HAV. The outcome for patients with FHF as the result of other causes of viral hepatitis is much less favorable.

**Causes**

Numerous causes of FHF exist, but viral hepatitis and acetaminophen overdoses are the most common.

The cause remains unknown in as many as 15% of patients.

Viral hepatitis is a common cause of hepatic failure.

**Pathophysiology**

The development of cerebral edema distinguishes FHF from portosystemic encephalopathy, although certain mechanisms appear to be common to both clinical entities.

Briefly, hyperammonemia may be involved in the development of cerebral edema. Another consequence of FHF is multisystem organ failure, which often is observed in the context of a hyperdynamic circulatory state that mimics sepsis (low systemic vascular resistance); therefore, circulatory insufficiency and poor organ perfusion possibly either initiate or promote complications of FHF.

Many hemodynamic features of FHF may be mediated by elevated systemic concentrations of nitric oxide, which acts as a potent vasodilator. However, in this setting, cytokine profiles are deranged, and a distinct possibility exists that neurohumoral effects mediate extrahepatic organ dysfunction, with the circulatory manifestations simply representing epiphenomena. Elevated serum concentrations of bacterial endotoxin, tumor necrosis factor-a, and interleukin-1 and interleukin-6 have been found in FHF, but the specific roles of these inflammatory mediators are unclear.

The development of liver failure represents the final common outcome of a wide variety of potential causes, as the broad differential diagnosis suggests. A complete discussion is beyond the scope of this article, and the reader is directed to consult the literature dealing specifically with these underlying etiologic factors. However, mechanisms of acetaminophen hepatotoxicity are worth discussing briefly.

As with many drugs that undergo hepatic metabolism (in this case, by cytochrome P-450), the oxidative metabolite of acetaminophen is more toxic than the drug. An active metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), appears to mediate much of the damage to liver tissue by forming covalent bonds with cellular proteins. Therefore, the presence of highly reactive free radicals following acetaminophen ingestion poses a threat to the liver parenchyma, but it usually is addressed adequately by intrahepatic glutathione reserves. The reduced glutathione quenches the reactive metabolites and acts to prevent nonspecific oxidation of cellular structures that may result in severe hepatocellular dysfunction.

This mechanism fails in 2 different yet equally important settings. The first is an overdose (accidental or intentional) of acetaminophen. This simply overwhelms the hepatic stores of glutathione, allowing reactive metabolites to escape. The second and less obvious scenario occurs with a patient who consumes alcohol regularly. This does not necessarily require a history of alcohol abuse or alcoholism. Even a moderate or social drinker who consistently consumes 1-2 drinks daily may sufficiently deplete intrahepatic glutathione reserves. This results in potentially lethal hepatotoxicity from what is otherwise a safe dose of acetaminophen (below the maximum total dose of 4 g/d) in an unsuspecting individual.

**Histologic Findings**. Biopsy findings may be nonspecific, but in general, they depend on the underlying etiology. Panlobular necrosis generally is observed as a result of idiosyncratic medication-induced hepatitis leading to FHF. Centrilobular necrosis is typical of acetaminophen-induced FHF, but panlobular injury also may be observed. Viral hepatitis typically shows a panlobular injury and may be difficult to distinguish from medication-induced hepatitis. The presence of microvesicular steatosis suggests certain medications as a cause for FHF (valproic acid, salicylates in Reye syndrome) but also is observed in acute fatty liver of pregnancy.

**CLINICAL**

**History**

Clinical features may be self-evident and lead to a rapid diagnosis of ALF.

History is valuable for guiding appropriate interventions.

If the patient is incapacitated, closely question family members and friends.

Detail the date of onset of jaundice and encephalopathy, alcohol use, medication use (prescription and illicit or recreational), herbal or traditional medicine use, family history of liver disease (Wilson disease), exposure risk factors for viral hepatitis (travel, transfusions, sexual contacts, occupation, body piercing), and toxin ingestion (mushrooms, organic solvents, phosphorus contained in fireworks).

Determine if any complications have developed.

**Physical**

By definition, findings include jaundice and encephalopathy. The latter may be demonstrated to a varying degree.

In contrast to the typical patient with hepatic encephalopathy, hallucinations are somewhat more prevalent.

Development of cerebral edema ultimately may give rise to manifestations of increased intracranial pressure (ICP), including papilledema, hypertension, and bradycardia.

Patients may demonstrate massive ascites and anasarca due to fluid redistribution following the development of hypoalbuminemia.

Patients may not exhibit this initially if deterioration has been rapid, particularly if no fluid resuscitation has been performed.

Hematemesis or melena may complicate the presentation of FHF as a result of upper gastrointestinal bleeding.

This pattern is indistinguishable from septic shock. While this may be intrinsic to hepatic failure, considering the possibility of a superimposed infection (especially spontaneous bacterial peritonitis) is important.

**Lab Studies**

CBC count: Results may indicate thrombocytopenia.

These tests are used to determine the presence or severity of coagulopathy.

They are sensitive markers of hepatic synthetic failure but rarely in the setting of suspected FHF.

Hepatic enzymes

Levels of the transaminases often are elevated dramatically as a result of severe hepatocellular necrosis.

**Procedures:**

* Liver biopsy

A percutaneous liver biopsy is contraindicated in the setting of a coagulopathy. However, a transjugular biopsy can be performed in this setting if clinically indicated.

* Intracranial pressure monitoring

When establishing a diagnosis of intracranial hypertension or cerebral edema, this approach is frequently necessary and has value in guiding management.

Typically, extradural catheters are safer than intradural catheters. Intradural catheters are somewhat more accurate and, in the hands of a neurosurgeon experienced with their use, may be equally safe.

**TREATMENT**

**Diet**

Patients are, by necessity, nothing by mouth (NPO). They may require large amounts of intravenous glucose to avoid hypoglycemia.

When enteral feeding via a feeding tube is not feasible (eg, as in a patient with paralytic ileus), institute total parenteral nutrition (TPN).

Restricting protein (amino acids) to 0.6 g/kg body weight per day was previously routine in the setting of hepatic encephalopathy, but this may not be necessary.

**Activity**: Recommend bedrest.

**Medical Care**

The most important aspect of treatment is to provide good intensive care support. Recognizing the condition promptly and understanding its potential to require transplantation are essential. Monitoring for complications and instituting appropriate therapy are critical.

Use the standard method to manage portosystemic encephalopathy. Administer **lactulose** and/or **neomycin** to reduce ammoniagenesis

The most important issue is to consider, detect, and appropriately manage cerebral edema.

As a result of severe coagulation deficits, patients with FHF are prone to intracranial hemorrhages and subdural hematomas that must be considered in the evaluation.

**Management of increased ICP is as follows:**

Management is not unique to FHF, and the situation requires monitoring.

Use mannitol for primary treatment; however, it is contraindicated in renal failure. In this setting, consider treating with a barbiturate coma. However, try to avoid using sedatives because they impair accurate assessment of the patient's progress.

The exception may be in a patient with raised ICP who is extremely agitated (this further raises ICP). Raise the head of the bed 10-20° and avoid agitating the patient (noise, intratracheal suctioning).

**Manage renal failure as follows:**

Hemodialysis may significantly lower the mean arterial pressure such that cerebral perfusion pressure is compromised.

Continuous arteriovenous hemofiltration is preferred.

**Manage coagulopathy as follows:**

Patients with FHF may bleed from any percutaneous access site or minor abrasion, and extensive internal hemorrhage may occur.

Requirements for **fresh frozen plasma** and platelet replacements may be substantial, and this requires close monitoring, especially during planned procedures (eg, ICP monitor placement).