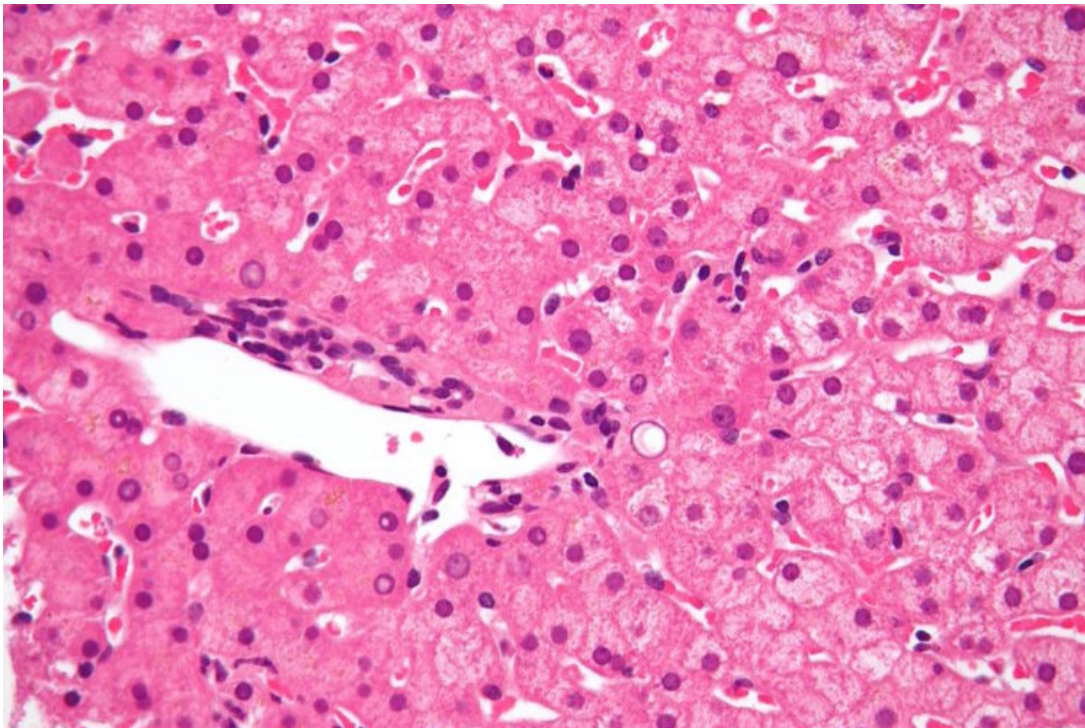


End-stage Liver Disease (ESLD) — Pathogenesis and Liver Transplantation

[See online here](#)

Approximately, 5.5 million people in the United States have liver cirrhosis. End-stage liver disease affects mainly the middle-aged population and is considered as the seventh commonest cause of death in the United States. The majority of these patients die due to the limited availability of donor livers. Several complications are encountered in end-stage liver disease and include ascites, hepatic encephalopathy, malnutrition and renal failure. Hepatocellular carcinoma is another possible complication in chronic liver cirrhosis.



Overview

End-stage liver disease (ESLD) refers to irreversible decomposition of liver function due to **chronic liver disease** or **acute liver failure**.

ESLD has several etiologies; the most common is **hepatitis C**. **Hepatitis B**, other viral infections, and **excessive alcohol intake** are also linked to **liver cirrhosis** and, eventually, ESLD. **Non-alcoholic steatohepatitis** is becoming a more common etiology for ESLD because of the expanding population of pre-diabetics and patients with metabolic syndrome. Less common causes of ESLD include **Wilson's disease** and **alpha-1 antitrypsin deficiency**.

Epidemiology of End-Stage Liver Disease

Approximately 5.5 million Americans have chronic liver disease, which is a staggering number. Chronic liver disease is ranked as the 12th most common cause of death in the United States, and ESLD is the 7th most common cause of death in the middle-aged population. Many patients with cirrhosis die in their fifth or sixth decade of life.

Once ESLD is diagnosed, a **3-month mortality score** is calculated using the **Model for End-Stage Liver Disease (MELD)**, which gives a score between 6 to 40, with 40 being the most severe disease. A score ≥ 30 indicates **fulminant hepatic failure**, which has a mortality rate approaching 80%.

Pathogenesis of End-Stage Liver Disease

The current consensus is to restrict the term ESLD to patients with liver failure accompanied by **renal abnormalities**.

Patients with chronic liver disease go into hepatic failure when there is greater than 90% loss of the hepatic cell mass, resulting in **synthetic and excretory liver failure**. The liver will not be able to cope with **albumin** and other protein synthesis demands, **the international normalized ratio (INR)** will be markedly impaired, and these patients will have high **bilirubin** levels.

Pathophysiological changes in liver cirrhosis



Image: "Macroscopic image of micronodular (liver) cirrhosis caused by alcohol consumption" by Amadalvarez - Own work, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Many patients with EDLD have pre-existing **liver cirrhosis**; therefore, it is important to consider the pathological aspects implicated in liver cirrhosis.

Liver cirrhosis results from a chronic process of liver injury and repair. This process eventually leads to **hepatic fibrosis**, loss of normal hepatic structure, and **vascular abnormalities**.

Pathophysiological aspects and cirrhosis complications

ESLD is associated with liver cirrhosis complications, which are directly implicated in morbidity and mortality. The causes include **distorted blood flow** and **increased**

portal vein pressure, loss of hepatic cell mass, and uncontrolled injury/repair processes.

Varices and **ascites** are caused by the increased portal pressure occurring in liver cirrhosis. Synthetic and excretory liver impairment can cause **hepatic encephalopathy** and **spontaneous bacterial peritonitis**.

Hepatocellular carcinoma is associated with uncontrolled hepatocyte injury and repair processes that are found in chronic liver disease, mostly due to **viral hepatitis**.

Clinical Presentation and Management of End-Stage Liver Disease

Ascites



Image: "Liver cirrhosis with ascites, marked" by James Heilman, MD - Own work, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Ascites is the most common complication of chronic liver disease and carries a high risk of mortality and recurrent hospitalization. Approximately 50% of patients with chronic liver disease will have ascites over a period of 10 years.

The first step in examining a patient presenting with ascites is to inquire about any previous history of liver cirrhosis since it is implicated in 85% of cases. Other conditions which can, but are less likely to, cause ascites include **heart failure**, **nephrotic syndrome**, and **thyroid disease**, which must be ruled out.

On physical examination, you should look for signs of liver disease such as **spider angiomas**, **dilated periumbilical veins**, a **distended jugular vein**, or fetor hepaticus, a distinct ammonia-like smell. More specific signs of ascites include **flank bulge** and **abdominal distension** with a **flattened umbilicus**. Percussion would elicit a dull note due to fluid accumulation in the abdomen.

Diagnostic work-up of ascites in ESLD



Image "Ascites" by James Heilman, MD. Lizenz: (CC BY-SA 3.0)

A **diagnostic paracentesis**, where a needle is passed through the abdominal wall and fluid is collected, should be the first step in the diagnostic work-up of these patients.

The **serum-ascites albumin gradient** is defined as the difference between ascetic and serum albumin concentration. If the serum-ascites albumin gradient is larger than or equal to 1.1 g/dL, **portal hypertension** should be suspected.

Protein content in the ascetic fluid is, typically, below 2.5 g/dL in liver cirrhosis and above 2.5 g/dL in patients with heart failure or thyroid disease. **Ascetic fluid cell count** can also rule out **spontaneous bacterial peritonitis**, a possible complication of ascites.

If malignancy is suspected, **abdominal magnetic resonance imaging** is indicated.

Treatment of ascites in ESLD

The first step is to **restrict sodium intake** and prescribe **diuretics**, which are usually successful in patients with ascites due to elevated portal pressure. All patients, especially those with **alcoholic liver disease**, should be advised to stop drinking alcohol.

Therapeutic paracentesis should be done to alleviate ascites, but it is essential to treat the underlying cause in these patients. **Antiviral therapy** for hepatitis B and C, and **immunotherapy** for autoimmune hepatitis, should be attempted. Dietary sodium intake should be limited to 2 grams per day. Prescribing **spironolactone** with a **loop diuretic** is the current standard treatment.

Patients with ascites are at an increased risk of **renal failure**; therefore, renal toxic medications, such as angiotensin-converting inhibitors, should be avoided. Patients with **refractory ascites** may benefit from albumin infusions.

Instead of serial large-volume paracenteses, a **transjugular intrahepatic portosystemic shunt (TIPS)** is recommended in patients who do not respond to albumin infusions for ascites and is thought to affect survival. TIPS is contraindicated for patients with congestive heart failure, severe **tricuspid regurgitation**, severe **pulmonary hypertension**, or **polycystic liver disease**.

Spontaneous bacterial peritonitis (SBP)

SBP is a potentially fatal complication of ascites and can occur in up to 30% of patients with chronic liver disease and cirrhosis. *Escherichia coli* and *Klebsiella pneumoniae*, both gram-negative enteric organisms, are the most common causes of SBP.

Clinical signs of SBP in a patient with ascites include **new-onset fever**, abdominal pain, new-onset renal failure, diarrhea, and **paralytic ileus**.

Diagnosis of SPB

SPB is diagnosed if the patient has an **ascetic fluid polymorphonuclear leukocytes count of 250 cells/mm³** or more and a **positive ascetic fluid bacterial culture**.

A sample should be cultured the patient is started on antibiotics. A single antibiotic dose can render the result negative in up to 85% of the cases. It is also important to distinguish between secondary bacterial peritonitis and spontaneous bacterial peritonitis. In secondary disease, **leukocytosis** is more pronounced, multiple organisms are identified in the culture, protein content in the ascetic fluid is greater than 1 g/dL, and **lactate dehydrogenase** is high but lower than 50 mg/dL.

Treatment of SPB

Patients with SPB should receive empirical antibiotic therapy. The current standard treatment is cefotaxime 2 g IV, every eight hours for five days or ceftriaxone 1 g IV every 12 hours. Patients with SPB and ESLD should be treated with IV cefotaxime with albumin. Norfloxacin 400 mg daily can be used for secondary prophylaxis in SPB.

Hepatorenal syndrome (HRS)

In about 20% of cases, patients who are hospitalized because of cirrhotic ascites develop renal dysfunction. HRS can be classified into two types. **Type 1 HRS**, defined as a **doubling in serum creatinine** to more than 2.5 mg/dL in less than two weeks, is **associated with SBP** and other infectious complications with high mortality. **Vasoconstrictors** are the mainstay of treatment, which could be combined with albumin.

Type 2 HRS, on the other hand, is **associated with refractory ascites**. It has a slower progression with a serum creatinine level that is between 1.5 and 2.5 mg/dL.

Median survival in untreated type 1 HRS is approximately two weeks. For untreated type 2, median survival is around four months. Patients with HRS can be considered ESLD cases.

Varices



Image: "Esophageal ulcers after banding, posted in public domain with permission of patient." by Samir - own work, License: [Public domain](#)

Varices develop as a result of [portal hypertension](#).

Portal-venous circulation is connected to the systemic arteriovenous circulation at different points, such as the stomach, [esophagus](#), and rectum. When portal hypertension occurs, the veins in these areas can become engorged and enlarged, creating esophageal and gastric varices, which can manifest as **upper gastro-intestinal bleeding** if an enlarged vessel ruptures.

Varices can be found in up to 60% of patients with ESLD. When a diagnosis of liver cirrhosis is made, **screening esophagogastroduodenoscopy (EGD)** is indicated to monitor gastroesophageal varices. If the EGD did not identify any varices at this baseline, the examination should be repeated every two years.

Varices can be classified into large and small with 5 mm as the cut-off. Table 1 summarizes the **Child-Turcotte-Pugh cirrhosis classification system**.

Parameter	Points		
	1	2	3
Encephalopathy	—	Grade 1 or 2	Grade 3 or 4
Ascites	Absent	Diuretic Responsive	Diuretic Refractory
Albumin	> 3.5 g/dL	2.8 - 3.5 g/dL	< 2.8 g/dL
Bilirubin	1 - 2 mg/dL	2 - 3 mg/dL	> 3 mg/dL
Prothrombin Time Compared to Control	1 - 4 seconds	4 - 6 seconds	> 6 seconds
INR	< 1.7	1.8 - 2.3	> 2.3

Table 1: Child-Turcotte-Pugh (CTP) cirrhosis classification system. Class A has 5 to 6 points, class B 7 to 9 points and class C 10 to 15 points. Non-selective beta-blockers for small varices are highly recommended for class B and C patients as they are at high risk for variceal bleeding.

Primary and secondary prevention of varices

Unfortunately, there is no current prophylactic treatment for patients with liver cirrhosis without varices that will prevent varices from developing. Patients who have small esophageal varices, < 5 mm, should be prescribed a non-selective beta-blocker. If the patient develops ESLD, he or she should have an EGD performed annually.

Larger varices that do not bleed can be treated with non-selective [beta-blockers](#) and **endoscopic variceal ligation (EVL)**. EVL significantly lowers the risk of variceal bleeding.

Treatment of variceal bleeding

Any patient who presents with **upper gastrointestinal bleeding** and previous history of **liver cirrhosis** should be screened for variceal bleeding.

Intravenous line access, fluid therapy, and restoring hemodynamic stability are essential before any definitive therapy. **Blood transfusion** should be reserved for those with hemoglobin levels < 7 g/dL. At this acute stage, **terlipressin** should be administered for at least the next five days. **Antibiotics prophylaxis** with ceftriaxone is also recommended.

Once the patient is stabilized, **endoscopy** should be done and **EVL** should be used. If EVL is not possible, **endoscopic variceal sclerotherapy** can be attempted. When none of these techniques is available, temporary measures, such as **balloon tamponade** for the first 24 hours, or **TIPS** can be used.

Secondary prophylaxis against variceal bleeding can be achieved with **non-selective beta-blockers**, which can be **combined with isosorbide mononitrate**. EVL should also be performed on large varices to prevent secondary bleeding. About 60% of patients who do not undergo EVL will experience secondary bleeding within one year of the first bleed.

Portosystemic shunts, such as TIPS, can be used to lower the risk of rebleeding. However, such procedures do not affect survival and increase the risk of **hepatic encephalopathy**.

Hepatic encephalopathy (HE)

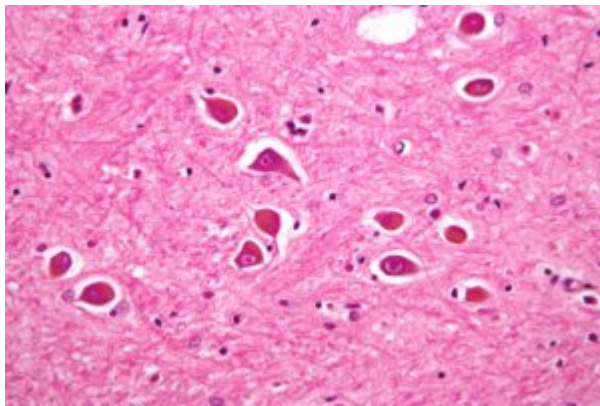


Image: "High magnification micrograph showing Alzheimer type II astrocytes, as may be seen in hepatic encephalopathy" by Nephron - Own work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

HE ensues when the patient develops **neuropsychiatric abnormalities** due to liver failure or as a side effect from portosystemic shunting. Several pathogenic mechanisms are thought to be involved in HE, including the **accumulation of ammonia in the blood** and the **accumulation of glutamine in brain astrocytes**.

There are no diagnostic criteria for HE. It is diagnosed by excluding other possible causes of encephalopathy, most importantly **hypoxia, hypercapnia, acidosis, uremia, strokes**, and **hypoglycemia**.

Patients with HE present with mental status impairment, **hyperreflexia**, and **asterixis**. HE can affect any domain of brain function, including cognition, intellect, emotions, and fine motor skills.

Diagnostic work-up for hepatic encephalopathy

Arterial blood ammonia levels correlate with HE severity, but certain precautions need to be taken while collecting the sample. A tourniquet should not be used, and the sample should be kept on ice and analyzed in less than 20 minutes.

Neuropsychometric tests can be used to define abnormalities in attention, visuospatial awareness, and fine motor skills in an objective approach.

Management of HE

Once the diagnosis of HE is confirmed, **supportive care** should be provided, and any precipitating cause, such as an upper gastrointestinal bleed or infection, should be treated.

Lactulose and **rifaximin** are prescribed and usually work in the first 48 hours, which can confirm the HE diagnosis. If the patient develops a recurrent HE episode, then protein intake should be limited to 1.0 to 1.5 g/kg/day over small meals, six meals per day. Patients with severe HE who are not responding to medication should be referred for **liver transplant evaluation**.

Liver Transplantation

Liver transplantation is the **definitive treatment for ESLD** and is usually lifesaving. More than 6,000 liver transplantation procedures are performed per year in the United States. **Chronic hepatitis C** is the most common etiology for ESLD. The current five-year survival, post-transplantation, is 74%.

When to refer a patient with ESLD for liver transplantation

The decision to refer a patient for a liver transplant is currently based on two possible criteria. Using a prognostic score approach, patients with a **MELD score of 10 or a CTP score of 7 or greater** should be referred for a transplantation center because the one-year survival rate is below 45%. Patients with **acute fulminant hepatic failure due to drug intoxication**, such as acetaminophen poisoning, are also possible candidates for liver transplantation.

The other criterion for a liver transplant referral is based on the **development of decompensated cirrhosis**. When the patient develops multiple cirrhosis-related complications, such as ascites, SBP, HE, and variceal bleeding, the decision to refer the patient to a surgical unit for evaluation for liver transplantation should be offered. Living donors for liver transplantation are possible because the liver can regenerate.

Conclusion

In summary, patients with ESLD are at risk of developing several complications, such as ascites, SBP, variceal bleeding, and HE. **Hepatocellular carcinoma** is also associated with liver cirrhosis. Patients who develop these complications are at high risk of mortality and should be referred for a liver transplantation consultation. Finally, management should focus on treating and preventing the recurrence of these complications.

References

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