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) happens as a result of chronic liver disease or acute liver failure.

Several etiologies have been described with hepatitis B being the most common etiology of ESLD. Hepatitis C, other viral infections and excessive alcohol intake are also linked to liver cirrhosis and eventually ESLD.

Due to the expanding population of pre-diabetics and patients with metabolic syndrome, non-alcoholic steatohepatitis is becoming a more common etiology for ESLD. Less common causes of ESLD include Wilson’s disease and alpha-1 antitrypsin.
Epidemiology of End-Stage Liver Disease

A staggering number of Americans have chronic liver disease, approximately 5.5 million, and chronic liver disease is ranked as the 12th commonest cause of death in the United States. ESLD is the 7th commonest cause of death in the middle aged population.

Once the diagnosis of ESLD is established, 3-month mortality score is calculated by the Model for End-Stage Liver Disease (MELD), which gives a score between 6 to 40 with 40 being the most severe disease. Many of the patients with cirrhosis die in their fifth or sixth decade of life. Patients with fulminant hepatic failure have a very high mortality rate that reaches 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 more than 90% loss of the hepatic cell mass, which results in synthetic and excretory liver failure. The liver will not be able to cope with albumin and other proteins synthesis demands, the INR will be markedly impaired and bilirubin will be high in these patients.

Pathophysiologica changes in liver cirrhosis

As the majority of the patients with end-stage liver disease have pre-existing liver cirrhosis, it is reasonable to have a look on the pathological aspects that are implicated in liver cirrhosis.

In order for liver cirrhosis to happen, a chronic process of liver injury and repair has to occur. The recurrent injury and repair process would eventually cause hepatic fibrosis, loss of normal hepatic structure and vascular abnormalities.
Pathophysiological aspects and cirrhosis complications

Another important aspect to address about ESLD is liver cirrhosis complications, which are directly implicated with mortality and morbidity. The different cirrhosis complications happen because of distorted blood flow and increased portal vein pressure, loss of hepatic cell mass, and uncontrolled injury/repair processes.

Varices and ascites can be explained by increased portal pressure in liver cirrhosis. Synthetic and excretory impairment of the liver can cause hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis.

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

Clinical Presentation and Management of End-Stage Liver Disease

Ascites

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

The first step in approaching a patient presenting with ascites is to inquire about any previous history of liver cirrhosis as it is implicated in 85% of the cases. Other conditions to exclude include heart failure, nephrotic syndrome and thyroid disease, which can all cause ascites but are far less likely.

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

Diagnostic work-up of ascites in ESLD
A **diagnostic paracentesis** where a needle is passed through the abdominal wall and fluid is collected should be performed as a 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 also expected to be less than 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** is also indicated to exclude **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 to prescribe **diuretics**, which is usually successful in patients with ascites due to an 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, C and **immunotherapy** for autoimmune hepatitis should be attempted. Dietary sodium intake should be limited to 2 grams per day. Currently, it is recommended to prescribe **spironolactone** with a **loop diuretic**.

Patients with ascites are at an increased risk of **renal failure** and 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, **transjugular intrahepatic portosystemic shunt (TIPS)** is recommended in patients who do not respond to albumin infusions for ascites and is thought to affect survival. If the patient has congestive heart failure, severe **tricuspid regurgitation**, severe **pulmonary hypertension**, or **polycystic liver disease**, he or she should not undergo a TIPS procedure.
Spontaneous bacterial peritonitis (SPB)

SPB 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 SPB include a new onset fever in a patient with ascites, abdominal pain, new onset renal failure, diarrhea and a paralytic ileus.

**Diagnosis of SPB**

The diagnosis of SPB is established if the patient has an ascetic fluid polymorphonuclear leukocytes count of 250 cells/mm$^3$ or more and a positive ascetic fluid bacterial culture.

Request for culture should be attempted before starting antibiotics as 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, the 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. Cefotaxime 2 g IV, every eight hours for five days or ceftriaxone 1 g IV every 12 hours is the standard treatment of SPB. In patients with SPB and ESLD, IV cefotaxime with albumin should be administered. Norfloxacin 400 mg daily can be used for secondary prophylaxis in SPB.

Hepatorenal syndrome (HRS)

20% of the patients hospitalized because of cirrhotic ascites are expected to develop renal dysfunction. HRS can be classified into two types. **Type 1 HRS** is defined as a doubling in serum creatinine to more than 2.5 mg/dL in less than 2 weeks and is associated with SBP, and other infectious complications. Type 1 HRS is associated with high mortality and vasoconstrictors are the mainstay of treatment which could be combined with albumin.

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

Median survival in type 1 HRS is approximately 2 weeks if not treated and for type 2 it is around 4 months. Patients with HRS can be considered as end-stage liver disease cases.

Varices
Varices develop as a result of portal hypertension.

The portal-venous circulation is connected to the systemic arteriovenous circulation in different points such as in 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 the enlarged vessels rupture.

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 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 classification system of cirrhosis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>—</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 3.5 g/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1 – 2 mg/dL</td>
</tr>
<tr>
<td>Prothrombin Time Compared to Control</td>
<td>1 – 4 seconds</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
</tr>
</tbody>
</table>

Table 1: Child-Turcotte-Pugh (CTP) classification system of cirrhosis. 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 in 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 to prevent varices from ever occurring. 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.

Large varices that do not bleed can be treated with non-selective beta-blockers and endoscopic variceal ligation (EVL). EVL was shown to significantly lower 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 suspected to have variceal bleeding.

**Intravenous line access, fluid therapy** and **restoring hemodynamic stability** is essential before any definitive therapy. **Blood transfusion** should be reserved for those with a hemoglobin level < 7 g/dL. At this acute stage, **terlipression** 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 are available, temporary measures such as with **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, which is estimated to be about 60% in the next year after the first bleed.

**Portosystemic shunts** such as TIPS can be used to lower the risk of rebleeding but one should keep in mind that 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](https://nephron.own-work.com/)

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

There are no diagnostic criteria for HE and it is a diagnosis of exclusion as other possible causes of encephalopathy need to be excluded. **Hypoxia, hypercapnia, acidosis, uremia, strokes, and hypoglycemia** are the most important to exclude.

Patients with HE present with mental status impairment, **hyperreflexia**, and **asterixis**. Any domain of brain function can be affected in HE and that includes cognition, intellelction, emotions, and fine motor skills.

**Diagnostic work-up for hepatic encephalopathy**
Arterial blood ammonia levels correlate with the severity of HE but certain precautions need to be taken while collecting the sample. A tourniquet should not be used and the sample should be kept in 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 and treatment of any precipitating cause such as an upper gastrointestinal bleed or infection should be done.

Lactulose and rifaximin are prescribed and usually work in the first 48 hours, which can confirm the diagnosis of HE. If the patient develops a recurrent HE episode, protein intake should be limited to 1.0 to 1.5 g/kg/day over small meals, 6 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 with chronic hepatitis C as the most common etiology for ESLD. Current five-year survival post-transplantation is at 74%.

When to go to liver transplantation for ESLD

The decision to go 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 1-year survival rate is below 45%. Patients with acute fulminant hepatic failure due to drug intoxication such as with acetaminophen poisoning are also possible candidates for liver transplantation.

The other criterion for a liver transplant is based on development of decompensated cirrhosis. When the patient develops multiple cirrhosis-related complications such as ascites, SBP, HE and variceal bleeding, the decision to refer 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 such complications are at high risk of mortality and should be referred to a liver transplantation consultation. Finally, management should be aimed towards treating and preventing the recurrence of these complications.

References

