Evaluation and Prognosis of Patients with Cirrhosis

Approach to the Evaluation of Patients with Cirrhosis

Overview: In an estimated 20 to 30% of patients with hepatitis C infection, chronic viremia results in inflammation followed by fibrosis and cirrhosis. Advanced fibrosis and early cirrhosis are not usually clinically detectable or symptomatic. As patients develop more extensive hepatic fibrosis, pressure begins to build within the portal system, potentially resulting in development of esophageal varices and splenic sequestration of platelets.

Defining Compensated versus Decompensated Cirrhosis: Once it has been established that a patient has cirrhosis, it becomes very important to determine whether they have compensated or decompensated cirrhosis. Patients with compensated cirrhosis do not have symptoms related to their cirrhosis, but may have asymptomatic esophageal or gastric varices. Patients with decompensated cirrhosis have symptomatic complications related to cirrhosis, including those related to hepatic insufficiency (jaundice), and those related to portal hypertension (ascites, variceal hemorrhage, or hepatic encephalopathy).

Importance of Distinguishing Compensated versus Decompensated Cirrhosis: Prognosis and survival is markedly better in patients with compensated cirrhosis than in those with decompensated cirrhosis (Figure 1). In addition, determining that a patient has decompensated cirrhosis can have major implications regarding management and prevention of cirrhosis-related complications, as well as consideration for a referral for liver transplantation evaluation. In general, any patient with decompensated cirrhosis should receive evaluation and medical care by a hepatologist. Some experts have proposed a 4-stage cirrhosis classification system that encompasses the spectrum of compensated and decompensated disease (Figure 2).
History and Physical Examination in Patients with Cirrhosis

Medical History

- **Alcohol Use:** Detailed quantitative information should be obtained from the patient regarding current and past alcohol use. A clinician's Pocket Guide for Alcohol Screening and Brief Intervention is available from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to inform clinicians how to take an appropriate alcohol history. Excessive alcohol use (greater than 40 grams per day in women and greater than 60 grams per day in men) in patients with chronic HCV has been associated with accelerated fibrosis progression. In addition, ongoing alcohol use will limit a patient’s HCV treatment options. Further, for those patients with chronic hepatitis C and more advanced liver disease ongoing alcohol use will limit their options to be considered for liver transplantation.

- **Illicit Drug Use Other than Alcohol:** Ongoing illicit drug use must be addressed. A patient continuing to use illicit drugs, particularly injection drugs, remains at risk for other bloodborne viruses and their access to HCV treatment will be limited. In addition, daily marijuana use has been associated with increased fibrosis progression. Further, for patients with more advanced cirrhosis, ongoing illicit drug use will limit their options for consideration to receive a liver transplantation.

- **Medication Use:** Medication use, including all non-prescription drugs and prescription drugs should be carefully reviewed. The patient should be counseled to limit potentially hepatotoxic drugs. LiverTox, a comprehensive database developed by the National Institutes of Health is an excellent resource to research the potential hepatotoxicity of medications. Reviewing medications is particularly important in patients with advanced liver disease since these patients are at higher risk to have an adverse reactions and these reactions may have more severe consequences due to their underlying compromised state. For example, a medication that causes nephrotoxicity may cause a patient with advanced cirrhosis to develop hepatorenal syndrome.

- **Comorbid Medical Conditions:** A thorough medical history should be documented including those diseases that might impact the progression of liver disease including HIV, hepatitis B, diabetes, obesity, and fatty liver. These diseases all take on increased importance in patients with chronic hepatitis C infection and cirrhosis.

- **Review of Symptoms:** In patients with cirrhosis it is critical to inquire about symptoms that would suggest complications of advanced liver disease, including abdominal girth swelling or tightness, lower extremity edema, jaundice, hematemesis or melena, and any signs of confusion.

- **Psychiatric History:** Chronic HCV may be associated with depression and coexistent depression may lead to poorer survival. Therefore, it is important to elicit a comprehensive mental health history in patients with more advanced liver disease.

Physical Examination

- **Body Mass Index (BMI):** Height, weight and calculation of body mass index (BMI) should be documented. Persons who are overweight (BMI greater than or equal to 25) or obese (BMI greater than or equal to 30) are at risk for nonalcoholic fatty liver disease (NAFLD). In patients with chronic hepatitis C infection, NAFLD may contribute to and accelerate the development of cirrhosis.

- **General Inspection:** Wasting suggests advanced liver disease. Scleral icterus can usually be detected if the serum bilirubin level is greater than 3.0 mg/dL. Identifying jaundice is an important factor in determining if a patient has compensated liver disease. Lower extremity edema is a sign of advanced cirrhosis, as well as low serum albumin.

- **Peripheral Stigmata of Advanced Liver Disease:** Spider angiomata are most commonly seen on the anterior chest, neck, face and upper thorax. Palmar erythema, gynecomastia, and testicular atrophy are often seen in advanced liver disease.

- **Abdominal Examination:** Examination of the abdomen may help in determining the size of
the liver and the presence of splenic enlargement, but the accuracy of physical examination in assessing organ size is limited. The most useful physical examination findings in confirming ascites are the presence of a fluid wave and shifting dullness. The absence of flank dullness on exam is a good predictor of the absence of ascites. In one study, the probability of ascites without flank dullness was less than 10%.

- **Mental Status Assessment:** A brief general assessment of patient mental status is appropriate at each visit. For patients with suspected altered or impaired mental status, a formal assessment for hepatic encephalopathy should be performed.
Classification and Prognostic Systems for Patients with Cirrhosis

Child-Turcotte-Pugh Score (CTP): The Child-Turcotte classification system was developed in 1964 to risk-stratify patients undergoing shunt surgery for portal decompression. In 1972, Pugh modified the Child-Turcotte system and it became known as the Child-Turcotte-Pugh (CTP) score. Although empirically derived, the CTP has been shown to accurately predict outcomes in patients with cirrhosis and portal hypertension. Because it is simple and does not require complicated calculation, clinicians have widely used this tool to assess the risk of mortality in cirrhotic patients.

- **Calculation:** The CTP scoring system incorporates five parameters: serum bilirubin, serum albumin, prothrombin time, ascites, and grade of encephalopathy (Figure 3). Based on the sum of the points from these five parameters, the patient is categorized into one of three CTP classes: A, B, or C. Several on-line CTP Score Calculators are available that will automatically compute the CTP score based on the numbers entered.

- **Limitations:** The CTP score has several limitations. The score has limited discriminatory capacity and does not adequately segregate patients with progressively abnormal lab results. For example, a patient with a serum bilirubin of 20 mg/dL would be assigned the same number of points as a patient with a serum bilirubin of 3.5 mg/dL even though serum bilirubin is known to be an important prognostic indicator. Also, two of the five parameters (ascites and encephalopathy) must be subjectively interpreted. In addition, variceal hemorrhage, which is an important marker of hepatic decompensation, is not included in the definition of CTP class.

- **Clinical Use:** The CTP score is still widely used in the clinic and hospital setting as a simple prognostic tool. Studies involving cirrhotic patients have shown that patient CTP scores can estimate risk of death at 3-months (Figure 4) and 1 to 2-year survival (Figure 5). For patients with cirrhosis, most experts recommend assessing the CTP score at each clinical visit. Patients with cirrhosis and a CTP score of greater than or equal to 7 should be referred for a liver transplantation evaluation. Additional indications for a liver transplantation evaluation include a model for end-stage liver disease (MELD) score of greater than or equal to 10 or evidence of hepatic decompensation (ascites, jaundice, encephalopathy, or variceal bleeding).

**Model for End-stage Liver Disease (MELD):** The model for end-stage liver disease (MELD) score was originally developed based on survival data from patients who underwent elective transjugular intrahepatic portosystemic shunt (TIPS) procedure. Investigators then studied the MELD scoring systems in more diverse patient populations with cirrhosis and found it to be a good predictor of 3-month mortality in patients who did not have TIPS placed (Figure 6). The MELD score was adopted in 2002 by the United Network for Organ Sharing (UNOS) to prioritize allocation of deceased donor organs for liver transplantation. The MELD score for prioritization for liver transplant ranges from 4 to 60 points. The higher the MELD score, the lower the 3-month survival (Figure 7). For example, a patient with a MELD score less than or equal to 15 has a predicted 3-month survival of 95% while a patient with a MELD score of 30 has a predicted 3-month survival of only 65%.

- **Calculation of MELD Score:** The MELD score, which estimates the survival probability of a patient with end-stage liver disease, is based on three commonly obtained laboratory parameters: serum bilirubin, serum creatinine, and international normalized ratio (INR) (Figure 8). Several on-line MELD Score Calculators are available, including the MELD Calculator from the Organ Procurement and Transplantation Network, that will automatically compute the MELD score based on the numbers entered.

- **Limitations:** The MELD score may be influenced by the method in which serum creatinine and INR are measured across laboratories. The MELD score has fewer limitations than the CPT score because it uses only objective data and can distinguish disease severity along a continuous spectrum.
• **Clinical Use:** The MELD score should be calculated on any patient with cirrhosis or advanced liver disease at each clinic visit. Patients with cirrhosis and a MELD score of 10 or greater should be referred for a liver transplantation evaluation. In addition, the indications for a liver transplantation evaluation also includes a CTP score of greater than or equal to 7 or evidence of hepatic decompensation (ascites, encephalopathy, jaundice, or variceal bleeding).
Compensated Cirrhosis

**Definition and Natural History:** Cirrhosis is considered to be compensated in the asymptomatic patient with or without gastroesophageal varices. Compensated cirrhotics are not jaundiced and have not yet developed ascites, variceal bleeding, or hepatic encephalopathy. Cirrhosis can remain compensated for many years. The transition from compensated to decompensated cirrhosis occurs at a rate of approximately 5 to 7% per year. The median survival of compensated cirrhotics has been reported to be 9 to 12 years.

**Management:** The major goal of managing patients with HCV and compensated cirrhosis is to treat the HCV infection. Patients with HCV-related cirrhosis who undergo treatment and achieve a cure have a dramatically decreased 10-year risk of all-cause mortality (Hazard ratio [HR] = 0.26), liver-related mortality or transplantation (HR = 0.06), hepatocellular carcinoma (HR = 0.19), and hepatic decompensation (HR = 0.07). In addition, all patients with cirrhosis should undergo surveillance for hepatocellular carcinoma with hepatic ultrasound every 6 months and they should have a screening endoscopy to determine whether they have gastroesophageal varices (and if present evaluation of the size of the varices).

**Gastroesophageal Varices:** Approximately 50% of persons with cirrhosis develop gastroesophageal varices. Screening for gastroesophageal varices with an upper endoscopy is an important preventive measure for all patients with cirrhosis. Patients found to have large varices or high-risk small varices should receive primary prophylaxis with either non-selective beta-blockers (NSBB) or endoscopic variceal ligation. Endoscopic variceal ligation is not recommended in patients with gastric varices. If no gastroesophageal varices are identified, the upper endoscopy should be repeated in 2 to 3 years.
Decompensated Cirrhosis

Definition and Natural History: Decompensated cirrhosis is defined by the development of jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy. A MELD score should be calculated for all patients with decompensated to better estimate the survival probability. In general, survival is poor in patients with decompensated cirrhosis and they should be considered for liver transplantation. Patients with ascites and variceal hemorrhage have a reported 1-year survival rate of less than 50%. Hepatitis C treatment in patients with decompensated cirrhosis has become possible with new interferon-free all-oral regimens.

Ascites: Ascites is the pathologic accumulation of fluid in the peritoneal cavity. It is the most common complication of cirrhosis. Following the development of ascites, a patient’s 1-year survival is only 50%. Ascites is caused by portal hypertension, which results in increased pressure within the splanchnic bed, and reduced protein production by the liver, which causes decreased oncotic pressure. Although treatment of ascites does not result in enhanced survival, it does improve the patient’s quality of life and decreases the risk of developing spontaneous bacterial peritonitis (SBP). Standard of care for the treatment of ascites involves sodium restriction and diuretic therapy with spironolactone alone or with furosemide.

Variceal Hemorrhage: The rate of bleeding with know varices is 12 to 15% per year. The mortality rate from each episode of variceal hemorrhage is approximately 15 to 20%. Acute variceal bleeding is a medical emergency and involves control of bleeding and prevention of complications. The risk of rebleeding within 1 to 2 years of the initial bleed is approximately 60%. It is extremely important that patients who survive an initial variceal hemorrhage start on prophylactic therapy to prevent future bleeds (see section above on Gastroesophageal Varices).

Hepatic Encephalopathy: Hepatic encephalopathy is thought to result from a buildup of toxic compounds generated by gut bacteria. These compounds are transported through the portal vein to the liver and metabolized and excreted immediately in a normal liver; in patients with cirrhosis, however, these toxins are not metabolized properly. Patients who develop hepatic encephalopathy may have subtle symptoms and the onset is often insidious. Hepatic encephalopathy represents a continuum from minimal to overt and can be episodic or persistent. The patient may have subtle and intermittent changes in personality, memory, concentration, and reaction time. Hepatic encephalopathy is a diagnosis of exclusion. The major goals of therapy include identification and correction of precipitating factors (such as infection and gastrointestinal hemorrhage) and reducing ammonia levels. Lactulose is the treatment of choice. It is a non-absorbable disaccharide that reduces ammonia by acidifying the colon and reducing colonic transit time.

Hepatorenal Syndrome: Hepatorenal syndrome is defined as renal failure in a patient with cirrhosis in the absence of intrinsic renal disease. The pathophysiology of hepatorenal syndrome is not completely understood, but it is thought to occur secondary to underfilling of the arterial circulation because of arterial vasodilation in the splanchnic circulation. This causes sodium and water retention in patients with renal vasoconstriction, which results in decreased renal blood flow and urinary output. Hepatorenal syndrome has been divided into 2 types: type 1 and type 2. Type 1 is rapidly progressive with a survival of approximately 2 weeks. The median survival for patients with Type 2 is 6 months.

Spontaneous Bacterial Peritonitis (SBP): SBP is the most common infection in patients with cirrhosis and ascites. SBP occurs in 10 to 20% of hospitalized patients with cirrhosis and in-hospital mortality for an episode of SBP is reported in the range of 10 to 20%. The recurrence rate of SBP after an initial episode is very high (approximately 70%). Patients who survive an initial episode of SBP should receive antibiotic prophylaxis.
Summary Points

- Patients with compensated cirrhosis do not have symptoms related to their cirrhosis, whereas those with decompensated cirrhosis have symptomatic complications related to cirrhosis (jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy).
- Most patients with chronic hepatitis C infection will have a normal physical examination, but those with advanced liver disease may have findings that suggest severe cirrhosis.
- The Child-Turcotte-Pugh (CTP) scoring system is based on five parameters (serum bilirubin, serum albumin, prothrombin time, ascites, and grade of encephalopathy); it is easy to perform and provides valuable prognostic information.
- The Model for End Stage Liver Disease (MELD) score provides accurate short-term prognostic information and should be calculated on any patient with cirrhosis or advanced liver disease.
- Patients with a CTP score greater than or equal to 7, a MELD score greater than or equal to 10, or decompensated cirrhosis should be referred to a hepatologist for a liver transplantation evaluation.
- Patients with cirrhosis who are asymptomatic are considered to have compensated cirrhosis, regardless of whether they have gastroesophageal varices.
- The major goal of managing patients with HCV and compensated cirrhosis is to treat the HCV.
- Decompensated cirrhosis is defined by the development of jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy.
- Survival is poor in patients with decompensated cirrhosis and they should be considered for liver transplantation.
References


- Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology. 2010;51:1445-9. [PubMed Abstract]


- Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-


Figures

Figure 1 One and Two Year Survival in Patients with Compensated or Decompensated Cirrhosis

This graph shows the markedly poorer survival in patients with decompensated cirrhosis when compared with those who have compensated cirrhosis.

Patients with cirrhosis can be subcategorized as having four stages, with stages 1 and 2 classified under Compensated category and stages 3 and 4 in the Decompensated category. The risk of death increases significantly with each more advanced stage.


**Figure 2 Four-Stage Cirrhosis Classification System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Compensated Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td>Clinical</td>
<td>No Varices No Ascites</td>
<td>Varices No Ascites</td>
</tr>
<tr>
<td>Death (at 1 Year)</td>
<td>1%</td>
<td>3%</td>
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</tbody>
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Figure 3 Child-Turcotte-Pugh Classification for Severity of Cirrhosis

The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.


<table>
<thead>
<tr>
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<th>Points*</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
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*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

- **Class A** = 5 to 6 points (least severe liver disease)
- **Class B** = 7 to 9 points (moderately severe liver disease)
- **Class C** = 10 to 15 points (most severe liver disease)
Figure 4 Mortality at 3 Months Based on Child-Turcotte-Pugh Score

Patients with higher baseline Child-Turcotte-Pugh scores have a marked increase in risk of death at 3 months than those with lower Child-Turcotte-Pugh scores.

**Figure 5 Survival at 1 and 2 Years Based on Child-Turcotte-Pugh Score**

This graphic shows a clear relationship of baseline Child-Turcotte-Pugh class (A, B, or C) and survival at 1 or 2 years. Without liver transplantation, patients with class C have a 1-year survival less than 50%.

Figure 6 3-Month Mortality Based on MELD Score

This graphic shows that with each 10-point increase in MELD score the 3-month mortality goes up significantly. Patients with a MELD score greater than 30 have a 3-month mortality that exceeds 50%.

Figure 7 Estimated 3-Month Survival Curve Based on MELD Score

This graphic shows the relationship of baseline MELD score and survival at 3 months. As the MELD score exceeds 15, the survival declines dramatically.

Figure 8 Model for End Stage Liver Disease (MELD) Score Calculator

The calculation for MELD score is complex as shown in this formula. Calculation of MELD score should be performed with a MELD calculator and many MELD calculators are available as a free online resource.


<table>
<thead>
<tr>
<th>Model for End Stage Liver Disease (MELD) Score</th>
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<tbody>
<tr>
<td>[ \text{MELD} = 3.78 \times \log_e \text{serum bilirubin (mg/dL)} + ]</td>
<td></td>
</tr>
<tr>
<td>[ 11.20 \times \log_e \text{INR} + ]</td>
<td></td>
</tr>
<tr>
<td>[ 9.57 \times \log_e \text{serum creatinine (mg/dL)} + ]</td>
<td></td>
</tr>
<tr>
<td>[ 6.43 \text{ (constant for liver disease etiology)} ]</td>
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NOTES:
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)