Background

Overview

In an estimated 20 to 30% of patients with hepatitis C virus (HCV) infection, chronic viremia results in inflammation followed by fibrosis and cirrhosis.\[1,2,3\] Advanced fibrosis and early cirrhosis are not usually clinically detectable or symptomatic.\[4\] 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.\[5,6\]

Defining Compensated and 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.\[7\] Patients with compensated cirrhosis often do not have signs or symptoms related to their cirrhosis, although they may have evidence of portal hypertension, such as esophageal or gastric varices.\[8,9,10\] In contrast, patients with decompensated cirrhosis have symptomatic complications related to cirrhosis, including those related to hepatic insufficiency (jaundice or hepatic encephalopathy), and those related to portal hypertension (ascites or variceal hemorrhage).\[11\]

Distinguishing Compensated versus Decompensated Cirrhosis

Prognosis and survival is markedly better in patients with compensated cirrhosis than in those with decompensated cirrhosis (\textit{Figure 1}) and (\textit{Figure 2}).\[12,13\] In addition, the presence of 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.\[14\] In general, any patient with decompensated cirrhosis should receive evaluation and medical care by a gastroenterologist or liver diseases specialist.\[7\] Some experts have proposed a 4-stage cirrhosis classification system that incorporates the spectrum of compensated and decompensated disease (\textit{Figure 3}).\[15,16\]
Evaluation of Patients with Cirrhosis

Once an individual is diagnosed with cirrhosis, there are key elements of the history, physical examination, and laboratory studies that need to be addressed and monitored.

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 infection has been associated with accelerated fibrosis progression.[17] In addition, for those patients with chronic HCV and more advanced liver disease, ongoing alcohol use will impact their eligibility for liver transplantation.

- **Illicit Drug Use Other than Alcohol**: Ongoing illicit drug use should be addressed. A patient who continues to use illicit drugs, particularly injection drugs, remains at risk for other bloodborne viruses and they can become reinfected with HCV after obtaining a sustained virologic response with treatment. In addition, for patients with more advanced cirrhosis, ongoing illicit drug use may impact consideration for liver transplantation.

- **Medication Use**: For individuals with cirrhosis, medication use, including all nonprescription 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 for clinicians to query the potential hepatotoxicity of medications. Reviewing medications is particularly important in patients with advanced liver disease since these patients may have altered metabolism of medications. In addition, if adverse medication reactions occur that affect the liver, persons with cirrhosis may have more severe consequences due to their underlying compromised hepatic function. 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 conditions can accelerate liver disease progression and all have enhanced importance in patients with chronic HCV 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 infection may be associated with depression and coexistent depression may lead to poorer survival.[18] Therefore, it is important to elicit a comprehensive mental health history.

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 HCV infection, NAFLD may contribute to and accelerate the development of cirrhosis.[19]

- **General Inspection**: Muscle 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 decompensated 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.[20] Palmar erythema, gynecomastia, and testicular atrophy are often seen in advanced liver disease. It is important to note that the absence of these
findings is not sufficient in ruling out cirrhosis.[20]

- **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.[8] 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 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.[21] In 1972, Pugh modified the Child-Turcotte system and it became known as the Child-Turcotte-Pugh (CTP) score.[22] Although empirically derived, the CTP has been shown to accurately predict outcomes in patients with cirrhosis and portal hypertension.[12, 23, 24] 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.[25]

• **Calculation**: The CTP scoring system incorporates five parameters: serum bilirubin, serum albumin, prothrombin time, severity of ascites, and grade of encephalopathy (Figure 4). 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. The CTP Calculator automatically computes the CTP score based on the numbers entered.

• **Limitations**: The CTP score has several limitations. First, the score has limited discriminatory capacity and does not adequately segregate patients with progressively abnormal lab results.[25, 26] 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 an extremely high serum bilirubin has greater prognostic impact.[26] Second, the CTP score gives equal weight to each of the five variables, which has been questioned by some experts.[25, 26] Third, two of the five parameters (ascites and encephalopathy) must be subjectively interpreted. Fourth, some important prognostic factors, including serum creatinine and variceal hemorrhage, are not included in the CTP scoring system.[25, 26]

• **Clinical Use**: The CTP score is still widely used in the clinic and hospital setting as a simple prognostic tool. Studies involving patients with cirrhosis have shown that CTP scores can estimate risk of death at 3 months (Figure 5), as well as 1 to 2-year survival (Figure 6).[12, 24] For patients with cirrhosis, most experts recommend assessing the CTP score at each clinical visit. The CTP score previously was used as a major criterion for liver transplantation evaluation, but it is no longer widely used for this purpose.[14]

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.[27] Investigators then studied the MELD scoring system in more diverse patient populations with cirrhosis and found it to be a good predictor of mortality in patients who did not have TIPS placed (Figure 7).[24, 28, 29] 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.[30] 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 8).[24] 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 9). The MELD Calculator will compute the MELD score based on the numbers entered. In January 2016, the MELD scoring system for donor allocation in the United States was further modified to incorporate serum sodium, using the MELD-Na equation for patients with MELD scores greater than 11.[31]

• **Limitations**: The MELD score may be influenced by the method in which serum creatinine and INR are measured across laboratories.[25, 26] 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, but it has been reported to have a misclassification rate of up to 10 to 20%.[25] In contrast with the
CTP score, which can easily be calculated at the bedside, the MELD generally requires access to a MELD calculator.[25]

- **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 15 or greater should be referred for a liver transplantation evaluation.[14]
Compensated Cirrhosis

Definition and Natural History

Cirrhosis is considered to be compensated in the asymptomatic patient with or without gastroesophageal varices; persons with compensated cirrhosis are not jaundiced and have not yet developed ascites, variceal bleeding, or hepatic encephalopathy.[12,32] Cirrhosis can remain compensated for many years.[32] The transition from compensated to decompensated cirrhosis occurs at a rate of approximately 5 to 7% per year.[12] The median survival of persons with compensated cirrhosis is approximately 9 to 12 years.[12]

Surveillance for Hepatocellular Carcinoma

The development of cirrhosis is the single most important risk factor for developing hepatocellular carcinoma (HCC).[33,34] Accordingly, all persons with cirrhosis (compensated or decompensated) should undergo surveillance for HCC with hepatic ultrasound every 6 months.[9,14] For patients with chronic HCV infection and cirrhosis, surveillance for HCC should continue after treatment for HCV, even if the individual obtained a sustained virologic response.[35] Some expert guidelines also recommend surveillance for HCC in persons with chronic HCV infection and advanced fibrosis (Metavir stage F3) or cirrhosis (Metavir stage F4).[35]

Screening for Gastroesophageal Varices

Among persons with cirrhosis, gastroesophageal varices develop at a rate of approximately 8% per year and varices may develop without initially causing any symptoms or bleeding.[32] All patients with cirrhosis should undergo screening for gastroesophageal varices with an upper endoscopy.[6,9] The subsequent management is based on the findings at endoscopy and is discussed in detail in Module 3, in the topic review Screening for Varices and Prevention of Bleeding.

Treatment of HCV in Patients with Compensated Cirrhosis

The major goal of managing patients with HCV and compensated cirrhosis is to treat the HCV infection.[36,37] Treatment of patients with compensated cirrhosis using newer direct-acting antiviral agents has been associated with sustained virologic response (SVR) rates of 90% or better.[38,39,40,41] 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).[37]
Decompensated Cirrhosis

Definition and Natural History

Decompensated cirrhosis is defined by the development of jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy.\cite{32} A MELD score should be calculated for all patients with decompensated cirrhosis to better estimate the survival probability. In general, survival is poor in patients with decompensated cirrhosis and they should be considered for liver transplantation. In addition, any patient with a MELD score of 15 or greater should be referred for liver transplantation evaluation.\cite{14}

Treatment of HCV in Patients with Decompensated Cirrhosis

Treatment of HCV in patients with decompensated cirrhosis has become possible with all-oral direct-acting antiviral agents. There are multiple HCV treatment studies that have shown high sustained virologic response rates in patients with decompensated cirrhosis.\cite{42,43,44,45} Treatment of HCV in persons with decompensated cirrhosis should be managed either by liver diseases specialist or with the very close involvement of a liver diseases specialist. For patients with chronic HCV and decompensated cirrhosis who are liver transplantation candidates, successful treatment of HCV with direct-acting antiviral therapy has occurred before and after transplantation.\cite{46,47,48} Given the complexity of these situations, decisions regarding the approach to HCV treatment and optimal timing of HCV treatment (before or after the transplant) should be made by the liver transplantation team.

Ascites

Ascites is the pathologic accumulation of fluid in the peritoneal cavity. It is the most common complication of cirrhosis and it is the first complication of cirrhosis in many patients.\cite{11,49} Following the development of ascites, a patient’s 1-year survival is only 50%. 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). This topic is addressed in detail in Module 3 in the topic review Diagnosis and Management of Ascites.

Spontaneous Bacterial Peritonitis (SBP)

Among persons with cirrhosis and ascites, SPB is the most common infection; it occurs in 10 to 20% of hospitalized patients with cirrhosis and is associated with an in-hospital mortality rate in the range of 10 to 20%.\cite{50} The recurrence rate of SBP after an initial episode is very high (approximately 70%) without prophylaxis. Patients who survive an initial episode of SBP should receive antibiotic prophylaxis. This topic is addressed in detail in Module 3 in the topic review Recognition and Management of Spontaneous Bacterial Peritonitis.

Variceal Hemorrhage

The rate of bleeding with known varices is 12 to 15% per year.\cite{9} The mortality rate from each episode of variceal hemorrhage is approximately 15 to 20%.\cite{51,52} Acute variceal bleeding is a medical emergency and involves control of bleeding and prevention of complications.\cite{9} The risk of rebleeding within 1 year of the initial bleed is approximately 60%.\cite{53} Thus, it is extremely important that patients who survive an initial variceal hemorrhage start on prophylactic therapy to prevent future bleeds.\cite{9} Recommendations regarding primary prophylaxis, secondary prophylaxis, and management of variceal bleeding are discussed in detail in Module 3 in the topic review Screening for Varices and Prevention of Bleeding.

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. This topic is addressed in detail in Module 3 in the topic review Diagnosis and Management of Hepatic Encephalopathy.

**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. Some experts have noted that use of beta-blockers in patients with decompensated cirrhosis may increase the risk of hepatorenal syndrome and many experts recommend discontinuing or avoiding the use of beta-blockers in patients with cirrhosis who have developed hepatorenal syndrome. Hepatorenal syndrome has historically been divided into 2 types: type 1 and type 2. More recently these terms have been replaced by the terms hepatorenal syndrome acute injury and hepatorenal syndrome chronic kidney disease, respectively.
Summary Points

- Patients with decompensated cirrhosis have complications related to cirrhosis (e.g. jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy).
- Most patients with chronic HCV infection will have a normal physical examination, but those with advanced liver disease may have findings that suggest 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 calculate 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 MELD score greater than or equal to 15, or decompensated cirrhosis should be referred to a hepatologist for a liver transplantation evaluation.
- Management of persons with chronic HCV infection and compensated cirrhosis should include treatment of the HCV infection.
- 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.
Citations


35. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Monitoring patients who are starting HCV treatment, are on treatment, or have completed therapy. [AASLD-IDSA HCV Guidance] -


41. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385:1075-86. [PubMed Abstract] -


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Figures

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

In this study, investigators analyzed data from 18 studies in patients with compensated cirrhosis and 23 studies in patients with decompensated cirrhosis to estimate 1- and 2-year survival rates. This graph shows the markedly reduced survival in patients with decompensated cirrhosis at baseline when compared with those who have compensated cirrhosis.

This study evaluated mortality rates in 4,537 persons with cirrhosis in the United Kingdom during the years 1987 and 2002. As shown in this graph, patients had an overall poor 5-year survival rate and persons with decompensated cirrhosis at baseline clearly had lower survival rates than those with compensated cirrhosis.


**Figure 2 One- and Five-Year Survival in Patients with Compensated or Decompensated Cirrhosis**
**Figure 3 Four-Stage Cirrhosis Classification System**

Patients with cirrhosis can be subcategorized by disease stage, with stages 1 and 2 classified under the Compensated category and stages 3 and 4 in the Decompensated category. In this figure, bleeding refers to variceal bleeding. The risk of death increases significantly with each more advanced stage.


<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>
</tr>
</tbody>
</table>
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>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
</tr>
</thead>
<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>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>or International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

<table>
<thead>
<tr>
<th>Class A</th>
<th>5 to 6 points</th>
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</thead>
<tbody>
<tr>
<td>Class B</td>
<td>7 to 9 points</td>
</tr>
<tr>
<td>Class C</td>
<td>10 to 15 points</td>
</tr>
</tbody>
</table>
Figure 5 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 6 Survival at 1 and 2 Years Based on Child-Pugh Score

This graphic shows a clear relationship of baseline Child-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 7 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 8 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 9 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 on line resource.


<table>
<thead>
<tr>
<th>Model for End Stage Liver Disease (MELD) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELD</strong> = 3.78 x log&lt;sub&gt;e&lt;/sub&gt; serum bilirubin (mg/dL) +</td>
</tr>
<tr>
<td>11.20 x log&lt;sub&gt;e&lt;/sub&gt; INR +</td>
</tr>
<tr>
<td>9.57 x log&lt;sub&gt;e&lt;/sub&gt; serum creatinine (mg/dL) +</td>
</tr>
<tr>
<td>6.43 (constant for liver disease etiology)</td>
</tr>
</tbody>
</table>

**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)