Evaluation and Prognosis of Persons with Cirrhosis

Background

Overview

In an estimated 20 to 30% of persons with hepatitis C virus (HCV) infection, chronic viremia results in inflammation, followed by fibrosis and cirrhosis.[1,2,3] Advanced fibrosis and early cirrhosis—at their early stages—are not usually clinically detectable or symptomatic.[4] As individuals develop more extensive hepatic fibrosis, physiologic complications can develop, such as increased pressure within the portal system, disruption in bilirubin metabolism, and reduced production of coagulation factor proteins.[5,6]

Defining Compensated and Decompensated Cirrhosis

Once it has been established that an individual has cirrhosis, it becomes very important to determine whether they have compensated or decompensated cirrhosis.[7] Persons 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, persons with decompensated cirrhosis often 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 persons with compensated cirrhosis than in those with decompensated cirrhosis (Figure 1) and (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 the potential need for a referral for liver transplantation evaluation.[14] In general, any person with decompensated cirrhosis should receive evaluation and medical care by a hepatologist or liver diseases specialist.[7] Some experts have proposed a 4-stage cirrhosis classification system that risk stratifies individuals according to the presence of ascites, esophageal varices, and variceal bleeding to differentiate and stage compensated and decompensated disease (Figure 3).[15,16]
Evaluation of Persons 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. In addition, for those individuals with chronic HCV and more advanced liver disease, ongoing alcohol use will impact their eligibility for liver transplantation.

- **Injection Drug Use**: Ongoing injection drug use should be addressed and supported. A person with chronic HCV and cirrhosis who continues to use injection drugs, remains at risk for acquiring other bloodborne viruses, such as HIV and hepatitis B virus (HBV), and they can become reinfected with HCV after obtaining a sustained virologic response with treatment. In addition, for persons 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. Of note, LiverTox does not provide detailed discussion on how medication likely impact persons with more advanced liver disease; for this inquiry, reviewing the drug package insert may be the best route. Reviewing medications is particularly important in individuals with advanced liver disease since they may have major alterations in the metabolism of medications that may place them at heightened risk of medication-related adverse reactions. In addition, if an adverse medication reactions causes hepatotoxicity, persons with cirrhosis may have more severe consequences due to their underlying compromised hepatic function. In addition, a medication that causes nephrotoxicity in a person with advanced cirrhosis may cause them 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 persons 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 or daytime somnolence.

- **Psychiatric History**: Chronic HCV infection may be associated with depression and coexistent depression may lead to poorer survival. 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 kg/m²) or obese (BMI greater than or equal to 30 kg/m²) are at risk for nonalcoholic fatty liver disease (NAFLD). In persons with chronic HCV infection, NAFLD may contribute to and accelerate the development of cirrhosis.

- **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 person has decompensated liver disease. Lower extremity edema may occur
with advanced cirrhosis and can potentially indicate low serum albumin.

- **Peripheral Stigmata of Advanced Liver Disease**: Spider angiomata, also known as spider nevi or spider telangiectasias, represent anomalous dilatation of cutaneous blood vessels and are among the earliest physical examination signs of cirrhosis. Spider angiomata are most commonly seen on the anterior chest, neck, face and upper thorax.[20] Palmar erythema, gynecomastia, and testicular atrophy are typically 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 persons with suspected altered or impaired mental status, a formal assessment for hepatic encephalopathy should be performed. The mental status assessment for hepatic encephalopathy is addressed in detail in the lesson Diagnosis and Management of Hepatic Encephalopathy.
Classification Systems for Persons 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 person 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 account for the degree of the abnormal lab results.[25,26] For example, a person with a serum bilirubin of 20 mg/dL would be assigned the same number of points as a person with a serum bilirubin of 3.5 mg/dL even though an extremely high serum bilirubin has poorer 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, the two clinical parameters—ascites and encephalopathy—are vulnerable to subjective interpretation. Fourth, some important prognostic factors, including serum sodium, 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 persons 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 persons 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 to predict the survival of persons with advanced liver disease who underwent an elective transjugular intrahepatic portosystemic shunt (TIPS) procedure.[27] Investigators then studied the MELD scoring system in other individuals with cirrhosis and found it to be a good predictor of mortality in persons 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 person with a MELD score less than or equal to 15 has a predicted 3-month survival of 95% while an individual 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 tests: 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] When compared with the CPT scoring system, the MELD score has an advantage because it only uses objective laboratory data, and it can distinguish disease severity along a continuous spectrum.[25,26] The MELD scoring system, however, has been reported
to have a misclassification rate of up to 10 to 20%.[25]

- **Clinical Use:** The MELD score should be calculated on any person with cirrhosis or advanced liver disease at each clinic visit. Individuals 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 experts also recommend surveillance for HCC in persons with chronic HCV infection and Metavir stage F3 (stage before cirrhosis) although the data in support of screening in this subpopulation is limited.[36]

Screening for Gastroesophageal Varices

Among persons with cirrhosis, gastroesophageal varices develop at a rate of approximately 8% per year and varices often develop without initially causing any symptoms or bleeding.[32] All patients with cirrhosis should undergo screening for gastroesophageal varices with an upper endoscopy to identify those individuals who may benefit from taking a nonselective beta-blocker for prophylaxis.[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.[37,38] 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.[39,40,41,42] 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).[38]
Decompensated Cirrhosis

Definition and Natural History

Decompensated cirrhosis is defined by the development of jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy.[32] The survival of persons with decompensated liver disease is significantly lower than in those with compensated disease. A MELD score should be calculated for all persons with decompensated cirrhosis to better estimate the survival probability and to determine eligibility for transplantation. Evaluation for transplantation should be considered once a person with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, variceal hemorrhage, or hepatic dysfunction with a MELD score of 15 or greater.[14]

Treatment of HCV in Patients with Decompensated Cirrhosis

Treatment of HCV in persons with decompensated cirrhosis has become possible with all-oral direct-acting antiviral agents. Moderately high rates of sustained virologic response rates have been demonstrated with NS5A and NS5B combination DAA therapy in persons with decompensated cirrhosis.[43,44,45,46] 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 individuals 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.[47,48,49] 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 and a manifestation of portal hypertension in cirrhosis. It is the most common and often the first complication of cirrhosis for many individuals.[11,50] Following the development of ascites the estimated 1-year survival is only 50%. Although treatment of ascites does not result in enhanced survival, it does improve the individual’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, SBP is the most common infectious complication; it occurs in 10 to 20% of hospitalized persons with cirrhosis and is associated with an in-hospital mortality rate in the range of 10 to 20%.[51] The recurrence rate of SBP after an initial episode is very high (approximately 70%) without prophylaxis. Persons 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.[9] The mortality rate from each episode of variceal hemorrhage is approximately 15 to 20%.[52,53] Acute variceal bleeding is a medical emergency and involves control of bleeding and prevention of complications.[9] The risk of rebleeding within 1 year of the initial bleed is approximately 60%.[54] Thus, it is extremely important that persons who survive an initial variceal hemorrhage start on prophylactic therapy to prevent future bleeds.[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.[55] These compounds are transported through the portal vein to the liver and metabolized and excreted immediately in a normal liver. In persons with cirrhosis, however, these toxins are not metabolized properly. Individuals 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 person with cirrhosis in the absence of intrinsic renal disease.[56] 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.[57] This causes sodium and water retention, with renal vasoconstriction, which results in decreased renal blood flow and urinary output. Some experts have noted that use of beta-blockers in persons with decompensated cirrhosis may increase the risk of hepatorenal syndrome and many experts recommend discontinuing or avoiding the use of beta-blockers in persons with cirrhosis who have developed hepatorenal syndrome.[58,59,60] Hepatorenal syndrome has historically been divided into 2 types: type 1 and type 2.[56,57,61,62] More recently these terms have been replaced by the terms hepatorenal syndrome acute injury and hepatorenal syndrome chronic kidney disease, respectively.[57,63]
Summary Points

- Persons with decompensated cirrhosis have complications related to cirrhosis (e.g. jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy).
- Most individuals 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 person with cirrhosis or advanced liver disease.
- Individuals with a MELD score greater than or equal to 15, or decompensated cirrhosis should be considered 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 persons with decompensated cirrhosis, and they should be considered for liver transplantation.


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References


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.

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

Patients with cirrhosis can be subcategorized by disease stage, with stages 1 and 2 classified under 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.

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.

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.

Figure 10 Spider angiomata

Spider angiomata are enlarged cutaneous blood vessels that resemble the appearance of spider. Compression of the central aspect of the lesions causes the entire lesion to blanch; with release of compression the blood quickly refills and the red color reappears.

Illustration by Jared Travnicek, Cognition Studio