

Prospective Management of Cirrhosis

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Abstract: An increasing number of patients are presenting with cirrhosis; thus, understanding and taking a prospective approach to their management is becoming essential. Cirrhosis is the final common pathway for many causes of chronic liver disease. Mortality rates dramatically increase when patients progress from compensated to decompensated cirrhosis. Close monitoring and early intervention is needed to delay this progression and improve survival once complications do arise. Patients should be monitored for clinical deterioration and worsening of laboratory values, and care should be taken to ensure adequate nutrition and avoidance of hepatotoxic medications. Susceptible patients may require immunization. Family members should be screened for contagious and inheritable causes of liver diseases, and screening for hepatic encephalopathy, varices, and hepatocellular carcinoma should be routinely performed. Prophylaxis against spontaneous bacterial peritonitis should be instituted in high-risk patients, and referral for liver transplantation should be made at the appropriate time.

Cirrhosis is responsible for more than 27,000 deaths annually, making it the 12th leading cause of mortality in the United States.¹ The most common causes of cirrhosis in the United States are alcoholic liver disease and chronic viral hepatitis. In the next decade, cirrhosis from fatty liver may emerge as one of the major indications for liver transplantation in this country. Cirrhosis represents a clinical spectrum in which patients are asymptomatic at one end and at the other end they have manifestations of hepatic decompensation, including variceal bleeding, ascites, hepatic encephalopathy, and hepatorenal syndrome. The results of a recent survey of practicing gastroenterologists in a major metropolitan city revealed variability in the adherence to established guidelines in the management of cirrhosis.² Morbidity and mortality rates rise dramatically when complications of cirrhosis develop; thus, it is important for practitioners to take an active role in the prospective management of the cirrhotic patient rather than just manage complications when they arise.

Keywords

Cirrhosis, prevention, screening

Table 1. Child-Turcotte-Pugh Scoring System

Variable	Points		
	1	2	3
Encephalopathy (grade)*	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1–2	2–3	>3
For primary biliary cirrhosis: bilirubin (mg/dL)	1–4	4–10	>10
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged) OR international normalized ratio	1–4 <1.7	4–6 1.7–2.3	>6 >2.3

Reprinted from Murray KF, Carithers RL Jr.³

*See Table 3.

Class A=5–6 points; Class B=7–9 points; Class C=10–15 points.

Initial Assessment

Once a diagnosis of cirrhosis is established, the focus should be to estimate the severity of hepatic injury. A comprehensive history and physical examination should note symptoms such as fatigue, pruritus, bleeding, and episodes of confusion or mood disturbances; review concurrent medical illnesses and medication use; and assess for ascites, splenomegaly, pedal edema, and asterixis. Initial laboratory studies should consist of a complete blood count (CBC) to check for anemia and thrombocytopenia; a comprehensive metabolic panel (CMP) to detect hyponatremia, renal insufficiency, aminotransaminase levels, bilirubin, protein, and albumin; coagulation studies (prothrombin time [PT] and international normalized ratio [INR]) to assess liver synthetic function; and alpha-fetoprotein (AFP) to screen for hepatocellular carcinoma (HCC). An imaging study such as ultrasound should also be performed at baseline for future comparison and to screen for HCC as well as for ascites.

Two widely used clinical staging methods for patients with cirrhosis are the Child-Turcotte-Pugh (CTP) system and the model for end-stage liver disease (MELD) system. The MELD has replaced the CTP system for allocation of organs for liver transplant because the former more accurately predicts mortality. The CTP system utilizes 3 quantitative variables (bilirubin, albumin, PT or INR)

Table 2. Model for End-Stage Liver Disease (MELD) Scoring System*

$$\text{MELD score} = 3.78[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57[\text{Ln serum creatinine (mg/dL)}] + 6.43$$

*The lower limit of all values is 1, and the upper limit of creatinine is 4. If the patient received dialysis at least twice in the last 7 days, the creatinine is entered as 4.

INR=international normalized ratio.

and 2 qualitative variables (encephalopathy, ascites) to assign a score between 5 and 15 (Table 1). Patients with scores less than 7 (class A) have compensated cirrhosis, whereas those with scores of 7 or greater (class B/C) are considered decompensated. The MELD score utilizes only 3 quantitative variables (bilirubin, INR, creatinine) for a score between 6 and 40 (Table 2). Patients with MELD scores of 10 or greater are considered decompensated.³ Although the CTP and MELD have both been validated as acceptable predictors of mortality, neither correlates well with quality of life.⁴

Diet and Medication Considerations

Maintaining adequate nutrition is important in patients with cirrhosis. Malnourishment has been shown to cause a higher rate of complications and is an independent predictor of mortality.^{5,6} Protein-calorie malnutrition is found in 65–90% of patients with cirrhosis and almost 100% of candidates awaiting liver transplantation.^{7,8} Patients with cholestatic liver disease are subject to caloric depletion and deficiencies in fat-soluble vitamins, whereas those with noncholestatic disease predominantly experience protein depletion.⁹ Although the utility of temporary protein restriction in patients with acute encephalopathy unresponsive to medications has been recently debated, it is well established that those with acute or chronic encephalopathy that can be managed with medications should not be protein-restricted. All patients with evidence of encephalopathy should be instructed to consume 4–5 small meals per day as well as a late evening snack for optimal nitrogen balance.¹⁰

Patients with cirrhosis are prone to specific nutrient deficiencies. Decreased levels of vitamin A may lead to night blindness, which can be corrected with 25,000 units per day of vitamin A for 4–12 weeks.^{11,12} Persistent problems with vision in the dark may result from concomitant zinc deficiency, which can be corrected with 600 mg per day of zinc for 3 months.^{11,13} Zinc deficiency

has also been implicated in the pathogenesis of hepatic encephalopathy.¹³ Vitamin D and calcium deficiencies may result in osteomalacia or osteoporosis, and patients should receive 800 IU per day of vitamin D3 and 1 g per day of calcium indefinitely.¹⁴

Patients with ascites should adhere to a low-sodium diet (<2 g/day), but fluid restriction is not necessary unless there is concomitant severe hyponatremia (serum sodium <120–125 mEq/L).¹⁵ In patients with a poor clinical response, 24-hour urine sodium levels can be checked. If urinary sodium excretion is higher than the prescribed sodium intake, compliance with a low-salt diet should be questioned. Multiple case reports have described severe or fatal infections with the *Vibrio* species in patients with cirrhosis; thus, avoiding consumption of raw seafood is recommended.^{16,17}

As the liver is a major site for drug metabolism, the use of any over-the-counter or prescription medications must be closely monitored. Nonsteroidal anti-inflammatory drugs should be avoided, as they may predispose patients to bleeding (by inhibiting platelets) and renal failure (due to decreased renal prostaglandin production) and have been rarely reported to cause 10-fold increases in transaminase levels.¹⁸ Doses of acetaminophen should be restricted to 2 g per day.¹⁹ The use of other medications, particularly those that are metabolized by the cytochrome P450 system (eg, benzodiazepines, warfarin, morphine) should be carefully monitored.

Screening of Family Members

It is essential to screen for causes of liver disease that are transmissible or inherited. Screening and identification of at-risk family members may potentially lead to earlier diagnosis and intervention. Appropriate counseling should be offered prior to any screening procedures.

Alpha-1-antitrypsin deficiency is a genetic condition that can lead to early-onset emphysema and hepatic impairment. There is variability in the severity and age of onset, and early diagnosis allows individuals to make informed lifestyle decisions, particularly regarding smoking, which increases the risk of severe pulmonary manifestations. Currently, screening of family members is performed by assessing alpha-1-antitrypsin phenotype and levels.²⁰

Hereditary hemochromatosis is an autosomal recessive inherited disorder of iron overload. Therapeutic phlebotomy, if instituted prior to the development of cirrhosis, can normalize life expectancy.²¹ Screening is recommended for all first-degree relatives of affected individuals with genotype testing based upon the proband.^{22,23}

Wilson disease is an autosomal recessive disorder of copper metabolism. Early treatment with copper chelators can slow or prevent multi-organ system failure, and

Table 3. West Haven Criteria for Semiquantitative Grading of Mental State

Grade 1	<ul style="list-style-type: none"> • Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impaired performance of addition
Grade 2	<ul style="list-style-type: none"> • Lethargy or apathy • Minimal disorientation for time or place • Subtle personality change • Inappropriate behavior • Impaired performance of subtraction
Grade 3	<ul style="list-style-type: none"> • Somnolence to semistupor, but responsive to verbal stimuli • Confusion • Gross disorientation
Grade 4	<ul style="list-style-type: none"> • Coma (unresponsive to verbal or noxious stimuli)

Adapted from Ferenci P, et al.³⁴

genetic screening of family members of affected individuals is recommended.²⁴ The American Association for the Study of Liver Diseases (AASLD) recommends screening of all first-degree relatives via liver function tests, CBC, ceruloplasmin level, 24-hour urine test for basal copper level, genotype testing based upon the identified proband, and slit-lamp examination for Kayser-Fleischer rings.²⁵

Hepatitis C virus (HCV), although more commonly acquired through blood inoculation, may also be transmitted through sexual contact. Studies suggest that spouses of patients with HCV who have ongoing viremia are at increased risk and should be screened with HCV antibodies. Children of mothers with HCV should also be screened.²⁶

Hepatitis B virus (HBV) can be transmitted sexually, horizontally, and vertically. Vertical transmission of HBV is an important etiology of chronic HBV infection leading to cirrhosis and HCC worldwide. Screening of all mothers, spouses, siblings, and children of affected individuals is recommended with serologic testing for hepatitis B surface antigen and hepatitis B core antibody.²⁷ Susceptible patients should be vaccinated.²⁸

Vaccination Recommendations

All patients with cirrhosis who are not already immune should be vaccinated against hepatitis A, hepatitis B, pneumococcus, and influenza. Although the risk of hepatitis A transmission is not higher among those with

cirrhosis than the general population, acute hepatitis A infection can lead to rapid clinical decompensation. The decision to test for immunity prior to vaccination should be based upon the likelihood of underlying immunity, as well as the costs of laboratory studies.²⁹ No adverse events are associated with the vaccination of an individual who is already immune. The current recommendations are for 2 doses of vaccination 6–12 months apart. The response to the vaccination differs according to the degree of liver disease. Patients with advanced liver disease, as well as those with obesity, advanced age, and a history of smoking, have a significantly decreased response rate to immunization. Postvaccination testing is currently not recommended,³⁰ though it can be considered in this group. The Centers for Disease Control and Prevention recommend 3 doses of hepatitis B vaccination at 0, 1, and 6 months. Because of the decreased seroconversion rate in cirrhotic patients, some physicians have advocated using a higher vaccine dose.³¹ Pneumococcus vaccination is recommended for all patients with cirrhosis. Those patients over the age of 65 who received their first dose before turning 65 should receive a second dose after 5 years. Patients who have concomitant HIV or chronic renal disease, are taking steroids, or have undergone liver transplantation should receive a second dose after 5 years regardless of age.³² Influenza vaccination is recommended annually. Patients with cirrhosis should receive the inactivated influenza vaccine rather than the live attenuated influenza vaccine.³³

Screening for Hepatic Encephalopathy

Patients without overt hepatic encephalopathy (HE) may still have minimal encephalopathy (Table 3).³⁴ Recent data show that minimal encephalopathy is common, and although the condition is subclinical, patients do have impairments in daily functioning and quality of life, and it may be unsafe for them to drive cars.^{35–37} There are currently no easily accessible methods for evaluating minimal encephalopathy. Some physicians have advocated a combination of psychometric tests (trail-making, block design, digit symbol) and neurophysiologic tests (brainstem auditory evoked potential, electroencephalography with mean dominant frequency).³⁸ Patients with evidence of overt HE should be treated and advised not to operate motor vehicles.

Screening and Management of Varices

Esophageal varices are present in 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis.³⁹ Each episode of bleeding carries a 20% mortality rate.⁴⁰ Untreated patients have a 70% rebleeding risk within 1 year.⁴¹ Varices are a direct con-

sequence of portal hypertension, and patients are at risk with portal pressures greater than 10 mmHg. The AASLD recommends classification of varices into 2 groups, small versus large, with 5 mm being the cutoff size. All patients should undergo upper endoscopy screening when they are diagnosed with cirrhosis. The frequency of repeat endoscopies depends upon the presence or absence of decompensation and endoscopic findings. Patients with small varices that show evidence of red wale signs (red marks or red spots) should be started on nonselective beta-blocker therapy. Those with small varices without red wale signs may also be treated with beta blockers, but the long-term benefits are unclear and no formal recommendations have been made. If beta-blocker therapy is initiated, no further screening endoscopies are needed. If beta-blocker therapy is not used, screening should be continued every 2–3 years unless there is evidence of hepatic decompensation, at which point screening should be increased to yearly. Patients with large varices should be treated with nonselective beta blockers, and further screening can be discontinued. Those patients who are unable to tolerate beta blockers should undergo endoscopic variceal ligation (EVL) every 1–2 weeks until the varices are obliterated. A screening upper endoscopy should be performed 1–3 months afterwards, and then every 6–12 months thereafter for surveillance of variceal recurrence.

Nitrates, either alone or in combination with beta blockers or EVL, surgical shunts, and sclerotherapy, should not be used as primary prophylaxis.^{42,43} Nonselective beta-blocker therapy can decrease overall upper gastrointestinal bleeding by 40%.⁴⁴ The dose of beta blockers should be titrated up to produce a 25% reduction in the patient's baseline heart rate, or until a resting heart rate of 55–60 beats per minute is reached.⁴⁵

Once patients have had an episode of variceal bleeding, further prophylaxis is warranted with nonselective beta-blocker therapy in addition to EVL. Repeat endoscopy should be performed 1–3 months after obliteration of varices and then every 6–12 months. Patients who are transplant candidates should be referred for liver transplantation evaluation at this time.

Approximately 20% of patients will have recurrent bleeding or persistent bleeding despite first-line therapy.⁴⁶ In this patient population, portal decompression should be considered with either a transjugular intrahepatic portosystemic shunt (TIPS) or a surgical shunt. Patients who bleed from gastric varices can undergo gastric variceal obliteration using tissue adhesives such as cyanoacrylate or sclerotherapy with agents such as ethanol. However, these modalities are not US Food and Drug Administration–indicated and may not be readily available. TIPS is often used for refractory gastric variceal

Table 4. Frequency of Outpatient Screening

Modality	Frequency (months)				
	3	6	12	24	36
Clinic visit					
• Compensated		X			
• Decompensated*	X				
Upper endoscopy					
• No varices					
– Compensated					X
– Decompensated			X		
• Small varices					
– Not on beta blockers				X	
– On beta blockers	No further screening				
• Large varices	No further screening				
Abdominal ultrasound		X			
Alpha-fetoprotein		X			
Laboratory work[†]					
• Compensated		X			
• Decompensated	X				

*Decompensation is defined as a Child-Turcotte-Pugh score ≥ 7 (class B/C), model for end-stage liver disease score ≥ 10 , or after the first complication (variceal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome).

[†]Complete metabolic panel, complete blood cell count, prothrombin time/international normalized ratio, albumin.

bleeding. Portal decompression is indicated for those patients who continue to bleed from gastric varices.

Screening for Hepatocellular Carcinoma

In patients with hepatitis C, the annual incidence of developing HCC is 1.4% in patients with compensated cirrhosis and 4% in patients with decompensated cirrhosis.⁴⁷ The AASLD recommends routine screening of all individuals with cirrhosis with an ultrasound every 6–12 months.⁴⁸ As the sensitivity and specificity of AFP in diagnosing HCC is low, it is generally agreed that AFP should not be used alone for screening purposes.⁴⁸ Cost-effectiveness studies have demonstrated that the combination of AFP plus ultrasound every 6 months is the most cost-effective screening strategy.⁴⁹

Prophylaxis for Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is a frequent complication of ascites, seen in up to 30% of patients with ascites who are hospitalized for any reason.^{15,50} Both the

AASLD and the International Ascites Club recommend performing a diagnostic paracentesis when clinically apparent ascites is first diagnosed.^{17,50} Ascites fluid should be sent for cell count with differential, total protein, and albumin. A concomitant serum albumin should be sent for calculation of the serum-ascites albumin gradient. Patients who have had a prior episode of SBP have a 1-year recurrence rate of 40–70%.⁵¹ Clinical trials show that SBP prophylaxis reduces morbidity and mortality.⁵² Prophylactic treatments include 400 mg per day of norfloxacin, 750 mg per week of ciprofloxacin, or 160 mg per day of trimethoprim/sulfamethoxazole for at least 5 days each week. All cirrhotic patients who present with upper gastrointestinal bleeding are at high risk for developing SBP and should receive prophylactic antibiotics for 7 days. Validated regimens include norfloxacin 400 mg orally twice daily, trimethoprim/sulfamethoxazole 160 mg orally twice daily, or ofloxacin 400 mg intravenously once daily.^{15,50}

High serum bilirubin (>2.5 mg/dL) and low ascites total protein (<1 g/dL) are also predictors of increased SBP. However, the use of primary prophylaxis in this group remains controversial.

Follow-Up Visits

Patients with well-compensated cirrhosis can be followed every 6 months, whereas those with decompensated cirrhosis should be seen every 3 months. At each visit, patients should be assessed for signs of clinical deterioration, including the development of ascites or hepatic encephalopathy. All preventive measures should be reviewed and updated appropriately, and all medication lists should be reviewed. Laboratory studies, including CBC, CMP, PT/INR, and albumin should be checked at each visit, and MELD and/or CTP scores should be recalculated.

Liver Transplantation

Liver transplantation is the ultimate treatment for patients with complicated liver disease. Patients who are otherwise transplant candidates should be referred for evaluation when their MELD score reaches 10 or their CTP score reaches 7. However, for most patients, the 1-year survival benefits outweigh the risks only when the MELD score is above 15.³ Other indications for referral are uncontrollable pruritus in cholestatic liver diseases, amyloidosis, development of type I hepatorenal syndrome, hepatopulmonary syndrome, or after the first major complication (ascites, encephalopathy, variceal bleeding). Patients with HCC confined to the liver with a single lesion less than 5 cm in size or no more than 3 lesions all less than 3 cm who are not candidates for surgical resection should also be referred for transplant evaluation.³ Recently, there has been increasing enthusiasm for expanding the criteria by which patients with HCC are accepted as candidates for liver transplantation.^{53,54}

Pretreatment viral load has important post-transplant prognostication. Both elevated hepatitis B and C viral levels predict early disease recurrence. Although antiviral therapy prior to liver transplant using oral nucleotides/nucleosides is safe for hepatitis B, the use of interferon in patients with decompensated liver disease from hepatitis C is not routinely employed, as it can lead to further hepatic decompensation.

If interferon therapy is contemplated in patients with any degree of hepatic decompensation, it should be administered by providers associated with a liver transplant center. Alternatively, liver transplant recipients can be treated for recurrent hepatitis C with interferon-based therapy.

Prognosis

The rate of transition from compensated to decompensated cirrhosis is approximately 5–7% each year, and median

survival for the former is more than 12 years compared to approximately 2 years for the latter.⁵⁵ In a systematic review of 118 studies, D'Amico and associates characterized 4 stages of cirrhosis.⁵⁵ Stage 1 is defined by the absence of esophageal varices and ascites, and the mortality rate is low at 1% per year. Stage 2 is characterized by esophageal varices without bleeding and without ascites, and the mortality rate is 3.4% per year. Patients in stage 3 have ascites with or without varices, but without bleeding. Mortality in this group is 20% per year. Patients in stage 4 have gastrointestinal bleeding with or without ascites, and 1-year mortality for this group is 57%. Stages 1 and 2 correspond to compensated cirrhosis, whereas stages 3 and 4 are decompensated.

Summary

Cirrhosis is a complex disease entity with a spectrum of clinical manifestations. Mortality rates dramatically increase when patients develop decompensated disease. Close monitoring (Table 4) and early intervention by the vigilant practitioner can delay disease progression and improve survival.

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