

The Gastroenterologist's Guide to Preventive Management of Compensated Cirrhosis

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Abstract: Despite advances in medical care, the prevalence and mortality associated with cirrhosis continue to rise. The majority of medical care and physician efforts are devoted to the management of decompensated cirrhosis and its complications of gastrointestinal hemorrhage, hepatic encephalopathy, and ascites; however, limited efforts are placed on the medical management of compensated cirrhosis. Patients with compensated cirrhosis carry a higher survival rate, and, when diagnosed early, may be screened for future decompensation. When possible, these patients can be treated for their underlying disease to prevent disease progression and avoid the need for liver transplantation. This article reviews the importance of early diagnosis, outpatient management of compensated cirrhosis, early screening for potential decompensation, and patient education.

Cirrhosis, the twelfth leading cause of overall death in the United States in 2016,¹ is a complication of long-standing liver disease. The condition is associated with gastrointestinal hemorrhage, hepatic encephalopathy, ascites, renal failure, and hepatocellular carcinoma (HCC), among other complications. The prevalence of cirrhosis has nearly doubled over the last decade, and the number of hospitalizations has similarly increased.^{2,3} The cost related to inpatient hospitalization has risen for all liver disease patients, but the cost accompanying acute-on-chronic liver failure has more than tripled during this time period.² Despite advances in medical care and additional expenditure on the treatment of decompensated cirrhosis, mortality related to cirrhosis rose between 2009 and 2016.³ There is a significant disparity in cost and clinical effort placed on the management of compensated vs decompensated cirrhosis. More effort should be focused on early diagnosis and preventive management of patients with compensated cirrhosis in order to delay or avoid decompensation and the rise in mortality associated with decompensation. This article reviews the importance of early diagnosis, outpatient management of compensated cirrhosis, early screening for potential decompensation, and patient education.

Keywords

Compensated cirrhosis, gastroesophageal varices, hepatocellular carcinoma, malnutrition, polypharmacy, patient education

Importance of Early Diagnosis

Cirrhosis is the final stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and formation of regenerative nodules. The gold standard for diagnosis continues to be liver biopsy,⁴ but it is an invasive procedure that carries risks of bleeding, infection, and mortality. Liver biopsy is not routinely required to diagnose cirrhosis, as clinical imaging, laboratory evaluations, and physical examination findings offer sufficient data to confirm the diagnosis. A nodular liver surface combined with laboratory findings of elevated bilirubin and international normalized ratio; thrombocytopenia; and physical examination findings of spider angiomas, palmar erythema, gynecomastia, jaundice, or asterix are adequate to make the diagnosis. Nevertheless, some of these manifestations may not be evident in patients with compensated cirrhosis, especially in individuals without portal hypertension. Multiple noninvasive modalities are currently available for early diagnosis of cirrhosis. Scores based on serologic tests can be incorporated into clinical practice, and include the aspartate aminotransferase-to-platelet ratio,⁵ Fibrosis-4 score,⁶ nonalcoholic fatty liver disease fibrosis score,⁷ and Enhanced Liver Fibrosis score.⁸ It is important to note that these scores have only been validated for patients with a specific etiology of liver disease and are not necessarily generalizable to all patients. Imaging modalities such as transient elastography⁹ or acoustic radiation force impulse imaging¹⁰ are becoming readily available alternative options in centers across the United States. Diagnostic options such as magnetic resonance elastography¹¹ are the closest in accuracy to a liver biopsy but are only available at limited centers across the United States.

Diagnosis of cirrhosis heralds an increased risk of liver-related morbidity and overall mortality.^{12,13} The median survival of patients with compensated cirrhosis is approximately 9 to 12 years, whereas the median survival among patients with decompensated cirrhosis drops significantly to approximately 2 years.^{12,14} Patients in the compensated stage are often asymptomatic and, therefore, remain undiagnosed, highlighting a need for more robust screening of advanced fibrosis among patients who are at risk of chronic liver disease. Diagnosing cirrhosis in patients who are still in the compensated stage offers the potential to improve or prevent progression of disease if the underlying cause of the liver disease is treatable (eg, abstaining from alcohol or taking antiviral treatments). Onset of decompensation, demonstrated by the development of ascites, hepatic encephalopathy, and/or gastroesophageal variceal hemorrhage, poses an increase in mortality (Figure 1).^{13,14} Thus, earlier diagnosis can help providers screen patients

for gastroesophageal varices while closely monitoring for other potential decompensations. Aside from decompensations, the severity of liver disease should be assessed with an available mortality predictor, such as the Model for End-Stage Liver Disease (MELD) with sodium and Child-Turcotte-Pugh (CTP) scores.¹⁵ An important complication not viewed as decompensation is the development of HCC, which requires ongoing screening from the time of diagnosis of cirrhosis. The rising burden of liver disease related to the late presentation of decompensated patients underscores the need to screen and diagnose cirrhosis early. An early diagnosis could also help clinical providers practice prospective medicine by screening patients for the aforementioned complications and educating their patients (Figure 2).

Management of Compensated Cirrhosis

Gastroesophageal Varices

At the initial diagnosis of cirrhosis, patients should be screened for gastroesophageal varices by undergoing esophagogastroduodenoscopy (EGD) (Figure 3).¹⁶ Gastroesophageal varices may be present in up to 50% of patients with cirrhosis, and new varices develop at a rate of 8% per year in patients without varices.^{16,17} Small esophageal varices progress to large varices at a rate of 8% per year, and gastroesophageal variceal hemorrhage occurs at a rate of approximately 12% to 15% per year.^{16,17} The mortality rate associated with each episode of gastroesophageal variceal bleeding is approximately 15% to 20%.¹⁶ Therefore, the goal of the initial EGD is to identify patients who are at highest risk of bleeding from gastroesophageal varices. If no gastroesophageal varices are identified, patients without existing decompensation can undergo repeat EGD in 1 to 3 years, which can be decided based on the presence or absence of ongoing liver injury from underlying liver disease. Patients with new or existing decompensations should undergo repeat EGD at onset of a decompensation and annually thereafter.

Bleeding Risk Factors The 3 factors that help identify patients who are at high risk of bleeding are varices that are large in size; appearance of red wale signs, cherry-red spots, or fibrin plug; and the severity of liver disease (CTP classes B and C). Patients with large varices, small varices with high-risk stigmata, or small varices in CTP classes B and C are at the highest risk of bleeding and should undergo primary prophylaxis to prevent an initial episode of gastroesophageal variceal hemorrhage.

Management Primary prophylaxis for the prevention of the first episode of variceal hemorrhage includes

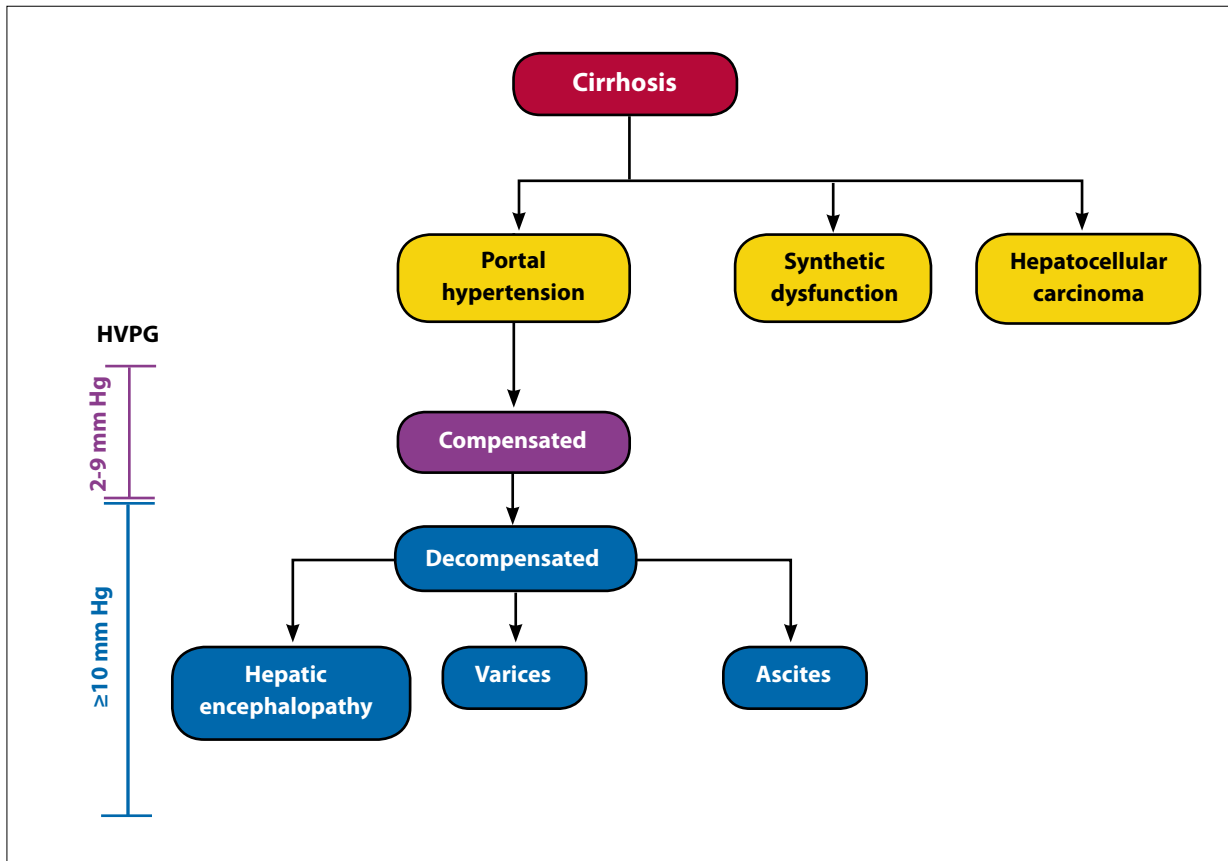


Figure 1. The natural course of cirrhosis. Complications of cirrhosis include portal hypertension, synthetic dysfunction, and hepatocellular carcinoma. Portal hypertension is considered clinically significant when hepatic venous pressure gradient (HVPG) is at least 10 mm Hg, leading to hepatic encephalopathy, varices, and ascites.

initiation of nonselective β blockers (NSBBs) or endoscopic variceal ligation (EVL). NSBBs prevent variceal hemorrhage by decreasing portal pressure via β_1 and β_2 blockade. β_1 blockade helps reduce cardiac output, while β_2 blockade leads to an unopposed α -adrenergic effect, thus indirectly causing splanchnic vasoconstriction. Together, these effects reduce the portal blood inflow. Traditional NSBBs include propranolol and nadolol. The treatment goal for traditional NSBBs is to use the maximal tolerated dose or until the heart rate reaches 55 to 60 beats per minute. Treatment should be stopped if systolic blood pressure is less than 90 mm Hg. Carvedilol is a newer NSBB and has a recommended fixed dose of 12.5 mg per day. Patients should be titrated to this dose and have their systolic blood pressure monitored, avoiding a pressure less than 90 mm Hg. After initiation of NSBBs, repeat EGD is not indicated unless NSBBs are stopped; if this treatment is stopped, patients should undergo EVL. However, NSBBs are beneficial

in select patients, defined by the window hypothesis. Therefore, a reduced dose should be considered based on blood pressure in patients with refractory ascites, spontaneous bacterial peritonitis, hypotension, hepatorenal syndrome, sepsis, and alcoholic hepatitis, as NSBBs reduce survival in these patients.^{18,19} Patients taking NSBBs often complain of weakness and fatigue, which can lead to noncompliance. In addition, NSBBs need to be used cautiously in patients with emphysema, asthma, and peripheral vascular disease.

EVL involves placing rubber bands around esophageal varices to obliterate them. Once EVL is pursued, endoscopy or banding is repeated every 2 to 8 weeks. When obliteration is confirmed, repeat endoscopy should be performed in 3 to 6 months to assess for recurrence. If the result is negative, endoscopy should be repeated every 6 to 12 months until liver transplantation or risks of the procedure outweigh the benefits due to cardiopulmonary comorbidities. Current guidelines recommend either

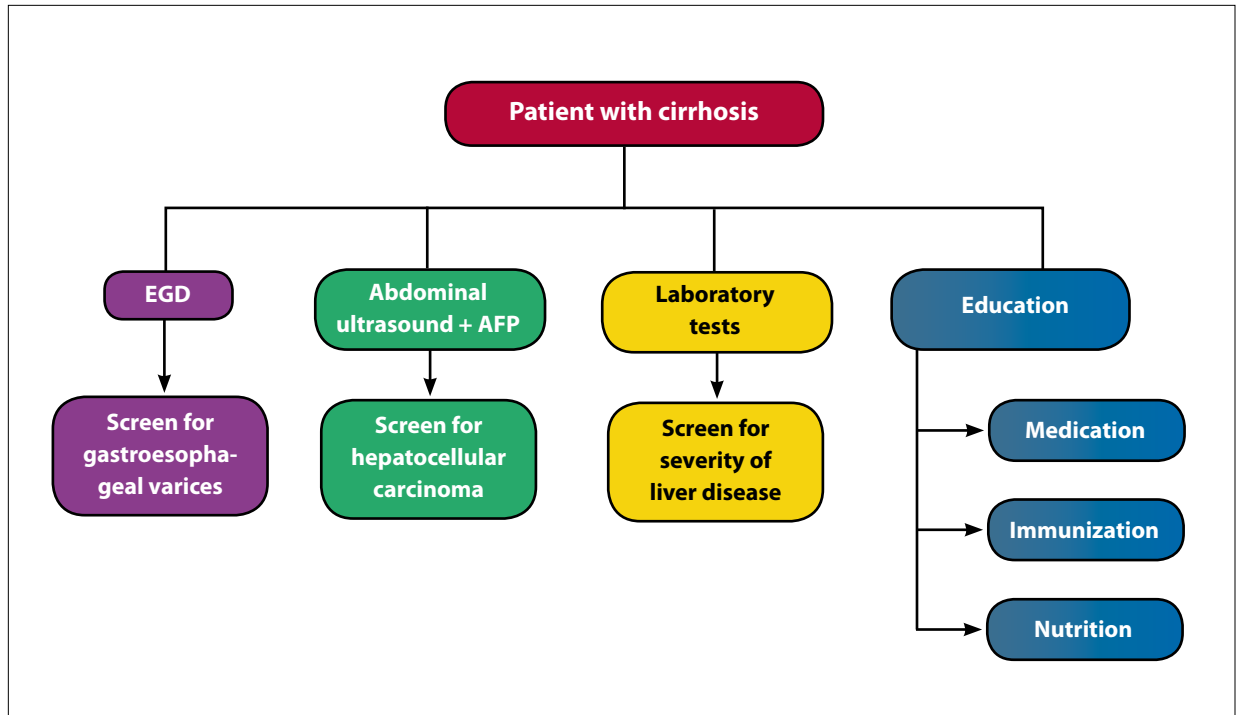


Figure 2. All patients with cirrhosis should be screened for gastroesophageal varices, hepatocellular carcinoma, and disease severity by assessing synthetic dysfunction using the MELD-Na score. Patients should be educated on the importance of nutrition and immunization and avoid hepatotoxic drugs.

AFP, α -fetoprotein; EGD, esophagogastroduodenoscopy; MELD-Na, Model for End-Stage Liver Disease with sodium.

NSBBs or EVL based on the patient's preference, center expertise, disease severity, and clinical contraindications.¹⁶

Hepatocellular Carcinoma

Surveillance All patients diagnosed with cirrhosis should undergo surveillance for HCC, as it improves overall survival.²⁰ The annual incidence rate of HCC is dependent on the etiology of liver disease and the severity of disease, with the rate rising significantly if patients have cirrhosis.²¹ Current guidelines recommend that patients should undergo surveillance every 6 months with an ultrasound, with or without serum α -fetoprotein (AFP).^{20,22} The addition of AFP improves overall survival.^{20,22} If an ultrasound is deemed inadequate due to reasons such as body habitus, then a contrast-enhanced multiphase study with either computed tomography (CT) or magnetic resonance imaging (MRI) should be pursued.²³

Diagnosis Lesions under the 10-mm threshold on ultrasound imaging may be followed up with a repeat ultrasound in 3 to 6 months. Lesions smaller than 10 mm have a low probability of malignancy and are difficult to diagnose, but the risk of malignancy substantially

rises for lesions 10 mm or larger in size.^{20,24} An AFP cutoff of more than 20 ng/mL should be considered a positive screen; however, some studies favor following longitudinal changes in AFP values, as a longitudinal change improves both the sensitivity and specificity of the study.^{25,26} Patients with a positive screen for lesions 10 mm or larger on ultrasound or with rising or elevated AFP levels should undergo a diagnostic study with a contrast-enhanced multiphase CT or MRI. Biopsies are rarely required in these cases. Each lesion should be interpreted via the CT/MRI Liver Imaging Reporting and Data System (LI-RADS) and assessed for size or growth of the lesion, arterial phase hyperenhancement, venous phase washout, and capsule appearance.²⁷ If a study is nondiagnostic on one modality, then an alternative modality should be pursued. For benign lesions (LI-RADS 1 and 2), repeat imaging should be pursued in 6 months. Indeterminate lesions (LI-RADS 3) should undergo repeat imaging in 3 to 6 months. LI-RADS 4 lesions suggest probable HCC, and imaging should be repeated within 3 months to assess for confirmation or changes. Liver biopsy should be considered in patients with liver lesions that do not have the typical features

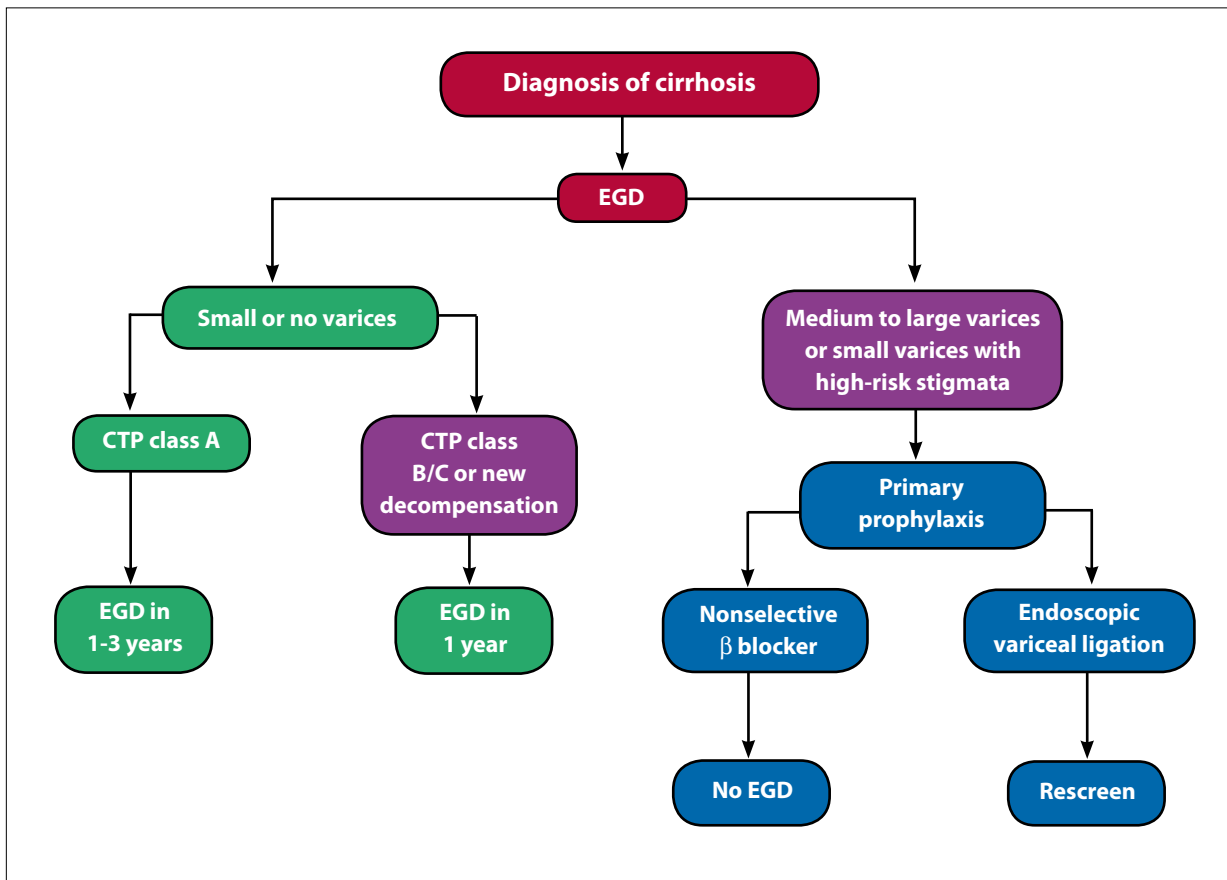


Figure 3. All patients with cirrhosis should be screened for varices and should undergo primary prophylaxis based on the size of their varices, high-risk bleeding stigmata, and severity of liver disease.

CTP, Child-Turcotte-Pugh; EGD, esophagogastroduodenoscopy.

for HCC or in patients with typical features for HCC in a noncirrhotic liver.²⁰ A LI-RADS 5 lesion is diagnostic of HCC.

Management Patients with confirmed HCC should be staged for tumor burden, metastatic disease, liver disease severity, and functional status. While multiple staging systems have been proposed in the literature to assess patients, guidelines suggest using the Barcelona Clinic Liver Cancer staging system.²⁰ Based on this staging system and the presence or absence of portal hypertension, patients may undergo liver resection or locoregional therapy while being considered for liver transplantation if their tumor burden is within the Milan criteria or if they could be downstaged to the Milan criteria. The Milan criteria are defined as a single lesion less than 5 cm in size, or up to 3 separate lesions with none larger than 3 cm in size.²⁰ Management of patients with confirmed HCC requires input from multiple consultants and is

best carried out in a multidisciplinary setting and using tumor board conferences, ideally at centers where liver transplantation is offered.

Patient Education

Nutrition

Malnutrition is a common finding in patients with cirrhosis and is an independent predictor of mortality.^{28,29} Aside from reduced survival, malnutrition and sarcopenia are associated with higher rates of complications, such as ascites, hepatic encephalopathy, and infections.³⁰⁻³² Alterations in metabolism that are similar in profile to an accelerated state of starvation reduce patients with cirrhosis to a chronic catabolic state, leading to a progressive decline in nutritional status as the severity of the liver disease worsens. Patients with cirrhosis should be screened for malnutrition and frailty, and, if at risk, they should undergo a detailed nutritional

assessment by a registered dietitian or nutrition expert. Patients who are at the highest risk of malnutrition are those who have decompensated cirrhosis. Management strategies should focus on improving the nutritional status of these patients with appropriate daily caloric and protein intake along with taking nutrition supplementation at bedtime, avoiding immobility, and encouraging exercise as tolerated.

Nutritional counseling should ideally be conducted by a multidisciplinary team to achieve goals of ideal daily energy and protein intake, as this approach has been demonstrated to improve survival and quality of life.³³ Bedtime snacks have been shown to improve muscle mass.³⁴ In patients with hepatic encephalopathy, protein restriction is not recommended.

Exercise

Exercise, particularly aerobic, is essential to improving aerobic capacity and cardiovascular fitness, leading to better outcomes in patients awaiting liver transplantation.³⁶ Resistance training improves muscle mass, which has been shown to decrease the risk of hepatic encephalopathy.^{35,36} Resistance exercises often require lower levels of cardio-pulmonary fitness and may be more feasible in patients with cirrhosis; however, proper nutritional assessment is crucial prior to initiating an exercise regimen, as rigorous physical activity in a nutritionally deficient patient can worsen muscle mass and lead to sarcopenia. As such, a multidisciplinary approach with a registered dietitian and an exercise therapist to tailor an individual plan for each patient based on his or her comorbidities would be ideal.

Safety of Alcohol and Medications

Alcohol Use Data are limited regarding a safe threshold of alcohol use for patients with cirrhosis. Given the hepatotoxic effects of alcohol, all patients with cirrhosis, regardless of the etiology of liver disease, should refrain from alcohol use. Even modest alcohol consumption is associated with worsening outcomes in patients with chronic liver disease and is related to an increased risk of developing HCC.^{37,38}

Prescription and Over-the-Counter Medications

Patients should avoid unnecessary over-the-counter health supplements due to the potential risk of drug-induced liver injury. Polypharmacy should also be avoided, and a thorough medical reconciliation should be performed at each clinic visit, including a review of nonprescribed medication intake. Acid-suppressive medications, in particular proton pump inhibitors (PPIs), are commonly prescribed to patients with cirrhosis and should be discontinued when their use is unnecessary, as PPIs are associated with an increased risk of infections such as

spontaneous bacterial peritonitis and *Clostridium difficile* colitis.^{39,40} Regarding analgesics, primary care physicians often avoid recommending acetaminophen, instead preferring the use of nonsteroidal anti-inflammatory drugs (NSAIDs) due to concerns of hepatotoxicity from acetaminophen.⁴¹ However, acetaminophen is safe to use at doses of less than 2 g per day in patients with cirrhosis, whereas NSAIDs should be avoided in patients with cirrhosis because of the risk of renal injury, hepatotoxicity, and gastrointestinal bleeding.^{40,41}

Cirrhosis is often associated with several vitamin deficiencies, such as folic acid, cobalamin (vitamin B12), thiamine (vitamin B1), and vitamin D. Given the low cost and low risk associated with multivitamin supplementation, daily consumption of a multivitamin should be encouraged in patients with cirrhosis.³⁵ Supplements containing vitamin A should be avoided due to its potential for hepatotoxicity. Vitamin D deficiency is associated with poor clinical outcomes; therefore, patients with cirrhosis should be screened and treated.^{42,43}

Immunizations

Infections are a common trigger for decompensations and can lead to acute-on-chronic liver failure. Infections and their subsequent deleterious effects can be prevented by early vaccination. Influenza and *Streptococcus pneumoniae* carry significant morbidity and mortality in patients with cirrhosis and are potentially preventable with an annual vaccination (influenza and 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine, respectively).^{44,45} Patients with cirrhosis should be vaccinated against hepatitis A and hepatitis B viruses if they have not attained natural immunity through exposure; however, the cost-effectiveness of the test-and-treat strategy is controversial and dependent on the patient population undergoing vaccination.^{46,47} Immunogenicity of vaccines is lower in decompensated cirrhosis, and patients should therefore be vaccinated at the time of initial diagnosis for the best results.^{48,49}

Screening for Routine Cancers and Associated Comorbidities

All patients with etiologies of cirrhosis, particularly cholestatic liver disease, are at risk of osteoporosis and should be screened with bone mass density measurements every 2 to 3 years.^{35,50} Age-appropriate colon cancer screening should be considered in patients with cirrhosis, and, when feasible, endoscopic procedures should be combined with gastroesophageal variceal screening in order to avoid excessive exposure to anesthesia. Patients should also undergo age-appropriate screening for breast cancer, cervical cancer, and prostate cancer. Compared to the general

population, patients with cirrhosis often ignore dental hygiene.⁵¹ Poor dentition can be a potential source of infections and septicemia, especially in the posttransplant setting. Patients with cirrhosis should be encouraged to undergo dental examinations every 6 to 12 months, and may need to undergo a bleeding risk assessment with viscoelastic testing.

Conclusion

In patients with cirrhosis, survival without liver transplantation is dependent on the timing of diagnosis and decompensation. Early diagnosis offers the opportunity to treat underlying causes, preventing progression of liver disease. Physicians should screen all patients with liver disease for advanced fibrosis and cirrhosis using noninvasive modalities. Serologic-based scores can be easily incorporated into the electronic medical record as a screening tool for primary care physicians, gastroenterologists, and hepatologists. By implementing early screening strategies, improving patient education, and offering preventive care, the economic burden of decompensated cirrhosis can be decreased, and survival and quality of life among patients with cirrhosis can be improved. Liver transplantation referral should be considered in patients with a MELD score of 15 or greater, in patients with HCC, or in patients with decompensated cirrhosis. There is a rising demand for liver transplantation despite an ongoing scarcity of donor grafts. The use of prospective medicine could decrease this demand.

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