

Medical Care of the Patient With Compensated Cirrhosis

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Abstract: The prevalence of liver disease and its complications is rapidly increasing in the United States. Gastroenterologists and hepatologists provide most of the medical care for patients with chronic liver disease and cirrhosis. While most gastroenterologists and hepatologists are comfortable managing the serious complications related to cirrhosis, many fail to provide the necessary education, prevention, and treatment for non-life-threatening problems associated with cirrhosis. Health-related quality of life has been found to strongly correlate with how well cirrhosis-related problems are addressed in the outpatient setting. This paper will review the outpatient management of patients with stable cirrhosis, including the surveillance and health maintenance recommendations necessary to monitor, prevent, or delay the onset of serious complications.

In 2002, chronic liver disease (CLD) was classified as the twelfth most frequent cause of death in the United States, accounting for 1.1% of all deaths or 27,257 deaths annually,¹ not a significant increase from 1998.² This number is probably too low as traditional methods used to calculate CLD mortality using death certificate data may underestimate hepatitis C–related CLD mortality.³ In fact, as a result of the hepatitis C virus (HCV) epidemic 20–30 years ago, it is expected that by the year 2020 the proportion of chronic HCV patients with cirrhosis will double from 16% to 32% and there will be a 180% increase in liver-related deaths.⁴ Although liver transplantation has emerged as the standard of care for patients with cirrhosis and advanced liver disease, the number of patients awaiting orthotopic liver transplantation has grown to 17,863 as of December 30, 2005.⁵ HCV accounts for the most common indication for transplant (4,970 in the waiting list), followed by alcoholic cirrhosis (1,096). Many patients with CLD are not eligible for liver transplantation or may not receive an organ transplant during their lifetime.

Most patients with CLD receive some or most of their medical care from gastroenterologists or hepatologists. Most gastroenterologists and hepatologists feel comfortable managing cirrhosis-related emergencies such as variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis. In contrast, gastroenterologists and hepatologists often fail to provide the necessary education,

Keywords

Cirrhosis, variceal bleeding prophylaxis, hepatocellular carcinoma surveillance, patient education

Table 1. Modified Child-Turcotte-Pugh Criteria

Parameter	Points Assigned to Laboratory Values and Signs*		
	1 Point	2 Points	3 Points
Total serum bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
Serum albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
INR	<1.70	1.71–2.20	>2.20
Ascites	None	Controlled medically	Poorly controlled
Encephalopathy	None	Controlled medically	Poorly controlled

* Based on total points: Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

INR = international normalized ratio.

prevention, and treatment for the non-life-threatening symptoms and complications that have been found to strongly correlate with health-related quality of life in patients with cirrhosis.⁶ This paper will review the surveillance and health maintenance recommendations that should be followed for every patient with compensated cirrhosis to delay or prevent the serious complications of cirrhosis.

Prognosis of Compensated Cirrhosis

Many chronic liver diseases run a steady course with gradual deterioration over time. The rate of progression is usually slow, particularly in the early phases of the disease, and then accelerates after complications of cirrhosis arise. The etiology of the liver disease is an important factor; alcoholic cirrhosis usually portends a worse prognosis in those patients who continue to drink alcohol after the diagnosis. Among patients with chronic HCV, a retrospective 5-year study of 384 patients showed that 91% were still alive at 5 years and the 10-year survival probability was calculated at 70%.⁷ Other investigators have assessed the 5-year risk of hepatocellular carcinoma (HCC) at 10% and decompensation at 15–20%.⁸ These patients will remain in the same practice for many years, providing an opportunity to intervene with prophylactic measures.

While a liver biopsy is often required to establish the diagnosis of cirrhosis in asymptomatic patients, the biopsy provides little information regarding the severity of disease. Several prognostic models have been developed to predict the course and outcome of CLD.⁹ Despite its multiple shortcomings, the Pugh modification of the Child-Turcotte criteria (CTP; Table 1)¹⁰ is the most frequently used model to establish the severity of liver disease in cirrhotic patients. Progression to a CTP score of 8 or higher signals early decompensation and should

prompt consideration for referral to a liver transplant center. The model for end-stage liver disease (MELD),¹¹ a recently developed prognostic model, is most useful in predicting short-term mortality in the setting of advanced liver disease among patients awaiting liver transplantation. In patients with compensated cirrhosis, longitudinal monitoring of the CTP score is recommended to detect evidence of early hepatic decompensation.

Patient Education

Patients with cirrhosis are often misinformed about their disease and its prognosis. Information is usually obtained from friends or the Internet and is often inaccurate, causing unnecessary anxiety for the patient. Educating patients with a chronic illness is not only good medical practice, it can also prevent adverse legal outcomes. Documentation in the patient's medical record that a discussion was held regarding the diagnosis of cirrhosis and necessary lifestyle modifications as well as providing the patient with educational written materials should be part of the care of every patient with cirrhosis. Five important points should be discussed during the initial visit: (1) alcohol use, (2) acetaminophen use, (3) the risk of *Vibrio vulnificus* infection, (4) the judicious use of vitamin and mineral supplements, and (5) the importance of weight control for overweight patients (Table 2).

Alcohol Use

All physicians should ask their patients about alcohol use, even if alcohol-related problems are unsuspected. Although most physicians routinely ask about alcohol use, only a small percentage use standardized screening questionnaires or refer patients to alcohol abstinence programs when alcohol abuse or dependence is suspected.¹²

There is no known safe threshold for alcohol use in patients with cirrhosis; for this reason complete abstinence

Table 2. Patient Education and Prophylactic Interventions

Alcohol use
• Abstinence advised
Acetaminophen use
• Preferred analgesic
• Use regular dose in early cirrhosis
• Limit total dose in advanced cirrhosis
<i>Vibrio vulnificus</i>
• Avoid raw or undercooked seafood
Vitamin and mineral supplements
• Limit vitamin A dose to 5,000 IU/day
• Avoid iron unless documented deficiency
Weight control
• Importance of hepatic steatosis in progression of liver disease
Immunizations
• Hepatitis A and B vaccines
• Polyvalent pneumococcal vaccine every 5 years
• Influenza vaccination yearly
Dental hygiene
• Prophylactic dental care every 6–12 months
Screening for osteoporosis

should be recommended. The alcohol-induced steatosis and iron overload¹³ that occur even with modest alcohol ingestion can worsen the severity and prognosis of the underlying cirrhosis and increase the risk for HCC.¹⁴

Acetaminophen Use

Acetaminophen use should be avoided in patients with cirrhosis who consume alcohol on a regular basis. Although early data indicated an increased risk of hepatotoxicity in alcoholics taking therapeutic doses of acetaminophen,¹⁵ other investigators suggest that these patients are at increased risk only if they ingest an overdose of acetaminophen¹⁶ or if they have underlying liver disease.

Among patients with cirrhosis who do not ingest alcohol on a regular basis, acetaminophen is the preferred analgesic and can be used safely at the recommended dose in patients with well-compensated cirrhosis. In a small study of 14 patients with cirrhosis, a mild decrease in the clearance of acetaminophen was noted when compared to controls; however, levels of acetaminophen metabolites were similar in controls compared to patients with liver disease. There was no significant difference in acetaminophen clearance between patients with well-compensated liver disease and those with advanced cirrhosis.¹⁷

Patients with cirrhosis have been found to have decreased levels of glutathione, possibly increasing the risk of acetaminophen toxicity. It is unlikely that this will result in a significant risk as low glutathione levels in patients with HIV, patients with chronic HCV, malnourished patients, and patients with cirrhosis has not been found to be a risk factor for acetaminophen toxicity.¹⁶

Patients with well-compensated cirrhosis can safely ingest the recommended dosage of acetaminophen (4 g over 24 hours in 4 divided doses). Until more information is available regarding the metabolism of acetaminophen in advanced decompensated liver disease, these patients should receive a maximum dosage of 2 g acetaminophen over 24 hours, with a maximum of 500 mg per dose. Because acetaminophen is a common ingredient in many over-the-counter products, patients should be encouraged to read the labels of all over-the-counter medications they take in order to avoid exceeding the recommended daily dosage of acetaminophen.

***V. vulnificus* Infections**

Vibrio vulnificus is an organism frequently found in saltwater, primarily along the warmer waters of the Gulf Coast and southern Atlantic Ocean, but has been reported in virtually all coasts of the United States. Infection with *V. vulnificus* usually causes a brief episode of gastroenteritis in noncirrhotic patients, but is often fatal in patients with cirrhosis, with iron overload, or who are immunocompromised such as liver transplant recipients.¹⁸

V. vulnificus infection may be acquired when eating contaminated raw or undercooked seafood such as oysters, or may cause a severe necrotizing cellulitis when a patient with skin abrasions is exposed to contaminated waters. *V. vulnificus* contamination is not related to fecal contamination of waters, thus it may be acquired even after consuming seafood harvested from “safe and approved” zones.

Patients with cirrhosis, particularly those with iron overload, should be advised not to consume raw oysters or any other type of raw or undercooked seafood. They should abstain from coming into contact with saltwater or brackish waters when skin abrasions are present.

Vitamin and Mineral Supplements

Patients with CLD often suffer from fatigue and turn to multivitamin supplements in an attempt to feel better. Certain vitamin supplements, particularly iron and vitamin A, may be harmful to the liver and patients should be cautioned about their use.

Vitamin A is stored in the liver in specialized cells known as stellate cells.¹⁹ When stellate cells are overloaded with vitamin A they transform into collagen-producing cells leading to liver fibrosis and worsening

portal hypertension. In contrast, vitamin A delivered as beta-carotene is safe. Patients should be advised not to consume supplements containing in aggregate more than 5,000 IU of vitamin A per day. Preferably, they should consume supplements that deliver vitamin A exclusively as beta-carotene, unless there is documented deficiency of vitamin A.

Iron is a hepatotoxic compound, promoting free radical formation and fibrogenesis potentially aggravating hepatocyte injury.²⁰ This risk is increased in patients with alcoholic cirrhosis, in whom iron overload is often present.²¹ Iron stores should be assessed in all patients with CLD by measuring the transferrin saturation and serum ferritin to screen for genetic hemochromatosis. In the absence of iron deficiency, patients with cirrhosis should be advised to use vitamin supplements that contain no iron.

Weight Control

As of 2002, it is estimated that 11 million people in the United States suffer from severe obesity.²² It is not surprising then, that many of our patients with CLD and cirrhosis are obese as well. Many studies have shown that most subjects with obesity have ultrasound evidence of fatty liver,²³ and up to 30% have histologic evidence of nonalcoholic steatohepatitis (NASH).²⁴ Until recently, simple steatosis was regarded as inconsequential; however, recent evidence suggests that the presence of fatty liver contributes to more rapid progression of other types of liver disease.²⁵⁻²⁷ Thus, when another liver disease is present, coexistent obesity or steatosis may worsen the prognosis. Furthermore, obesity adversely impacts the outcome of liver transplantation. Liver transplantation in patients with a body mass index greater than 35 is associated with decreased 30-day, 1-year, and 5-year posttransplant survival.²⁸ Morbid obesity is considered a contraindication to liver transplantation in many centers.²⁹

The benefits of weight loss for fatty liver disease have been documented.³⁰ Obese patients with cirrhosis should be counseled on the importance of weight loss and referred to appropriate weight loss programs. Available treatments for obesity include diet, exercise, behavioral modification, pharmacotherapy, and surgery, with varying risks and efficacies. Nonsurgical modalities, although noninvasive, typically result in relatively short-term limited weight loss, but should be tried prior to recommending surgery. Bariatric surgery in a patient with cirrhosis appears to be associated with more complications and increased early postoperative mortality.³¹ Rapid weight loss as seen after very low calorie diets or gastric bypass surgery is often associated with increased lobular liver inflammation and worsening of the liver disease.³² This effect is possibly mediated by an increase in the release of free fatty acids

after very rapid weight loss.²² More gradual weight loss, such as that seen with the newer laparoscopic adjustable gastric banding, has been demonstrated to provide improvement in liver histology, including decreased steatosis, necroinflammation, and fibrosis, without the risks associated with more rapid weight loss.³³

Surgical approaches to weight loss should only be considered in patients with well-compensated cirrhosis who are severely obese and have convincingly failed all other nonsurgical approaches to weight reduction. The presence of or a history of ascites, evidence of severe portal hypertension, large intra-abdominal varices, or significant hepatomegaly are all strong relative contraindications to bariatric surgery. A surgical procedure that will allow for controlled weight loss such as the adjustable gastric banding procedure is preferable to bypass procedures that may result in rapid uncontrolled weight loss that may worsen the underlying liver disease.

Preventive Measures

Immunizations

Acute hepatitis A,³⁴ hepatitis B,³⁵ and influenza³⁶ can be associated with significantly increased morbidity and mortality when they occur in patients with cirrhosis. These diseases are preventable and immunization should be considered. The hepatitis A vaccine has been found to be safe and effective in patients with CLD,³⁷ although the immunogenicity decreases when administered to patients with decompensated cirrhosis.³⁸ This highlights the importance of vaccination as soon as cirrhosis is diagnosed. Likewise, the efficacy of the hepatitis B vaccination is also blunted in patients with advanced cirrhosis. A double-dose accelerated hepatitis B vaccine schedule does not appear to be effective in overcoming this lack of response,⁴⁰ although some investigators report an increased response with this approach.³⁹ Testing for immunity against hepatitis A or B prior to vaccination and vaccinating only those who are susceptible is controversial.⁴¹ The cost-effectiveness of this approach depends on risk factors for hepatitis A and B infections and varies among different populations. The polyvalent pneumococcal vaccine is recommended for all patients over 65 years of age and those who suffer from a chronic debilitating illness at any age, including cirrhosis.

Dental Hygiene

Dental abscesses, severe gingivitis, and other types of serious oral infections are considered relative contraindications to liver transplantation. Oral infections usually give rise to septicemia during the immediate posttransplantation period when profound immunosuppression is induced. Most patients who are about to receive a liver

transplant are too ill to be subjected to the type of dental work required to correct these advanced problems. To prevent this unfortunate situation, patients on the liver transplant list are encouraged to undergo dental examination and prophylactic dental care every 6 to 12 months.

Screening for Osteoporosis

Osteoporosis is a well-recognized complication of all types of CLD, particularly among those with cholestatic liver diseases.⁴² Among patients with cirrhosis secondary to HCV or alcohol, 32% were found to have osteoporosis and only 35% had normal bone mass.⁴³ Most liver transplant recipients lose bone mass in the first 3 to 6 months after liver transplantation, with a high incidence of post-transplant fracturing in 30–40% of those with cholestatic disease.⁴² It is recommended that patients with chronic cholestasis, all patients with cirrhosis, and all potential liver transplant recipients undergo bone mass density measurement to screen for the presence of osteopenia or osteoporosis. Repeat screening is done at 2-year intervals in patients with normal bone density or mild osteopenia. For patients with osteoporosis or severe osteopenia, appropriate treatment measures should be instituted and response to therapy assessed by repeat densitometry.⁴²

Primary Prophylaxis of Variceal Hemorrhage

The presence of gastroesophageal varices is not universal among patients with cirrhosis. Esophageal varices are present in approximately 40% of patients with cirrhosis of the liver and 60% of those with ascites.⁴⁴ About one third of patients with documented varices will bleed within 2 years of diagnosis, with an associated mortality of 20–40% per episode.⁴⁵ Prophylactic treatment with nonselective beta blockers decreases the risk of the initial hemorrhage from esophageal varices by approximately 40% in individuals at increased risk for variceal bleeding.^{46,47} Nonselective beta blockers reduce portal pressure by reducing cardiac output and portal inflow by causing splanchnic vasoconstriction as a result of antagonism of the beta-2 receptors. The risk of variceal bleeding is markedly decreased if the hepatic vein wedge pressure gradient (HVWPG) can be lowered to less than 12 mm Hg.⁴⁸ Even among those who tolerate beta blockers, a reduction in HVWPG to less than 12 mm Hg is achieved only in a small group of patients, decreasing the efficacy of prophylaxis. Ideally the HVWPG should be measured to assess response to therapy and minimize the risk of bleeding; however, this is not practical in the clinical setting.⁴⁹

Treatment with nonselective beta blockers of all patients with cirrhosis has failed to show any benefit, probably because of the low bleeding rates in patients without varices,⁵⁰ and because the use of nonselective

beta blockers in patients without varices does not decrease the risk of developing varices.⁵¹ Thus, it is important to screen for varices and select patients at increased risk for bleeding, with the risk being highest for those patients with moderate to large varices on screening endoscopy.⁵² The presence of red signs (red wale markings, cherry red spots, and hematocystic spots) is associated with a further increased risk of bleeding.⁴⁵ Attempts have been made at improving selection of patients for screening endoscopy based on clinical, laboratory, and radiologic parameters predicting increased risk for variceal hemorrhage. Unfortunately, most noninvasive markers of severe portal hypertension lack sensitivity or specificity in selecting patients at high risk for variceal bleeding.⁵³ The American College of Gastroenterology practice guidelines⁵⁴ and the Baveno consensus workshop on portal hypertension⁵⁵ recommend endoscopic screening to detect varices in all patients with cirrhosis and no previous episodes of variceal hemorrhage. The recent development of esophageal capsule endoscopy may eventually replace routine fiber optic endoscopy for screening and grading of esophageal varices.⁵⁶

Because of the shortcomings associated with the use of nonselective beta blockers, other prophylactic interventions have been explored. Esophageal sclerotherapy for primary prevention of variceal bleeding is not recommended due to the increased complication rate associated with this procedure⁵⁷ and the lack of consistent benefit. Variceal ligation is associated with fewer complications compared to sclerotherapy and multiple studies have examined the role of ligation in primary prophylaxis with mixed results. When compared with propranolol for primary prophylaxis, band ligation was found to be equally effective⁵⁸ or superior⁵⁹ to the use of propranolol. Current evidence does not support the use of variceal ligation as the preferred method for primary prophylaxis; however, it should be the preferred option in patients with large varices who have contraindications to beta blockers or are unable to tolerate them.^{44,60} Nitrates are not tolerated by one-third of patients and have been found to be ineffective for primary prophylaxis.⁶¹

Based on available data, all newly diagnosed patients with cirrhosis and all other cirrhotic patients that are medically stable and willing to be treated prophylactically should undergo screening upper endoscopy. Patients at low risk for bleeding (no varices or small varices with no high risk stigmata) should undergo repeat surveillance endoscopy in 2 or more years.⁶² Patients at high risk for bleeding should be treated with nonselective beta blockers. Propranolol is generally used as a long-acting preparation with a starting dose of 60 mg/day. The dose is titrated to decrease the resting heart rate by 25% but not to less than 55 beats per minute.⁶³ The mean maintenance dose of propranolol required to reach this goal is 160 mg/day.

Table 3. Prophylaxis of First Variceal Bleeding: Recommendations

- Screening endoscopy for all patients with cirrhosis
 - No varices: repeat screening every 2–3 years
 - Small varices: screen every 1–2 years
 - Medium or large varices: treat with nonselective beta blocker
- Treatment should be continued indefinitely
- Endoscopic variceal ligation for patients with medium to large varices unable to tolerate beta blockers

Adapted from Bosch et al.⁶⁴

Evening administration is recommended to minimize some of the adverse events. About 30% of patients are unable to tolerate propranolol. Nadolol does not cross the blood-brain barrier and is generally better tolerated. The starting dose for nadolol is 20–40 mg/day, and the usual daily effective dose ranges from 20–240 mg/day.⁶⁴ Once initiated, therapy with nonselective beta blockers should be maintained indefinitely as when they are withdrawn the risk of variceal hemorrhage rises to pretreatment levels.⁶⁵ Those who are unable to tolerate nonselective beta blockers and are at high risk for bleeding should be considered for prophylactic endoscopic banding of varices.⁶⁶ The recommendations for prophylaxis of first variceal hemorrhage are summarized in Table 3.

Surveillance for HCC

Hepatocellular carcinoma is becoming an increasingly common cause of death in patients with cirrhosis. Epidemiologic data suggest that its frequency is sharply rising in the United States, most likely related to hepatitis C infection.⁶⁷ Among patients with cirrhosis and HCV infection, the annual incidence of HCC is 3–4%, with a higher risk probability found in patients older than age 55, patients with prothrombin activity of 75% or less, and patients with a platelet count of less than 75,000/mm³.⁶⁸ Alcohol, tobacco use, and obesity have recently been identified as risk factors for HCC in patients with cirrhosis.¹⁴

The purpose of surveillance is to recognize HCC at an early enough stage that the tumor can be treated or cured. Early diagnosis of HCC is possible through the use of imaging techniques such as ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) combined with regular measurement of serum alpha-fetoprotein (AFP) levels. Surveillance is controversial because it has not been established if it is associated with prolonged patient survival or if this approach is cost effective.⁵³ Recent reports, however, suggest that surveillance may increase survival compared to patients who present

with symptomatic HCC.^{69,70} In addition, using a Markov model for analysis, surveillance for HCC in patients with compensated HCV-related cirrhosis results in a gain in quality-of-life years at an acceptable cost, particularly if liver transplantation is prioritized for patients with early HCC.⁷¹ Regardless, surveillance for HCC in patients with cirrhosis has become a widely accepted practice.⁷²

The available data on tumor growth suggest that the time from an undetectable lesion to 2 cm is about 4–12 months.⁷³ Consequently, to detect tumors measuring less than 3 cm in diameter, the suggested interval for surveillance in patients with cirrhosis has been set at 6 months. Most authors recommend surveillance with AFP monitoring and US examination.

Periodic assessment of AFP levels alone has a poor sensitivity and specificity as a screening tool. It is often intermittently elevated in patients with HCV; AFP levels above the upper limit of normal were found in up to 23% of patients with cirrhosis and HCV despite no evidence of HCC.⁷⁴ Overall an elevated AFP level has a sensitivity of 39–64%, a specificity of 76–91%, and a positive predictive value of 9–32%.⁷² In African Americans with HCV cirrhosis, AFP levels are less sensitive in the detection of HCC compared to Caucasians.⁷⁵ AFP levels, however, still have a role for defining high-risk patients and guiding the frequency of imaging studies when levels are markedly elevated (>200 ng/mL). There is general agreement that AFP levels should not be used alone in screening patients with cirrhosis for HCC.⁷⁶

Ultrasound is a much better surveillance tool than AFP. Because of its lower cost compared to CT and MRI, US has emerged as the preferred initial imaging study for surveillance, with similar sensitivity and specificity to conventional CT.⁷⁷ Ultrasound, however, is operator-dependent, and it may be difficult to interpret in some circumstances such as in obese patients or heterogeneous liver parenchyma due to steatosis or micronodular cirrhosis, and is less likely to detect tumors that are isoechoic with the liver. Despite these limitations, US has an 85% sensitivity for tumors less than 3 cm⁷⁸ and is the most cost-effective imaging procedure for tumors surveillance.

Surveillance with US and AFP for HCC is now a well-established practice in the clinical management of patients with cirrhosis. An interval of 6 months between evaluations is recommended. Elevated levels of AFP should be interpreted cautiously as elevations often occur in the setting of cirrhosis without HCC. Levels greater than 400 ng/mL and possibly greater than 200 ng/mL are of most concern regarding HCC.

Guidelines for interpretation of US findings during HCC surveillance have recently been delineated⁷² and are summarized in Table 4. The detection of a small (<1 cm) liver nodule by US should trigger increased surveillance

Table 4. Surveillance for Hepatocellular Carcinoma

Right upper quadrant ultrasound examination and serum AFP levels every 6 months

- Nodule <1 cm: repeat ultrasound or complementary imaging study every 3 months
- Nodule 1–2 cm: consider image-directed biopsy of the lesion
- Nodule >2 cm: complementary imaging with triple-phase CT or MRI
 - Nodules with typical radiologic findings and AFP >200 ng/mL require no biopsy confirmation

Adapted from Bruix et al.⁷²

AFP = alpha-fetoprotein; CT = computed tomography; MRI = magnetic resonance imaging.

with US examinations every 3 months, as half of these nodules do not represent HCC. The finding of arterial enhancement in small (1–2 cm) liver lesions that demonstrate no growth with repeated examinations is not predictive for HCC in most cases.⁷⁹ Nodules between 1–2 cm that are confirmed by complementary imaging techniques (triple-phase contrast CT or MRI) should undergo biopsy as they are too small to be further characterized by imaging studies but big enough to potentially represent HCC. For lesions larger than 2 cm, imaging techniques with spiral CT or MRI using triple-phase contrast administration should be sufficient to detect the arterial hypervascularization typical of HCC. The finding of delayed hypointensity or “contrast wash-out” during the venous phase of the scan is a strong independent predictor for HCC regardless of the size of lesion.⁸⁰ Lesions larger than 2 cm with typical radiologic findings and an AFP level over 200 ng/mL usually do not require biopsy confirmation.

Medication Use in Patients With Cirrhosis

In cirrhosis, the clearance of drugs and other substances may be reduced. While drug-induced liver injury (DILI) is a common reason for withdrawing medications from further development or taking them off the market, the presence of liver disease does not necessarily increase the risk of DILI from a given medication. In fact, most drugs can be used safely in patients with underlying liver disease. The often-cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact.⁸¹

Not all drugs that are metabolized by the liver have decreased clearance in the presence of cirrhosis. Those drugs that are metabolized by conjugation to glucuronic acid rather than by cytochrome P450 (CYP) retain normal metabolism even in advanced liver disease.⁸² Thus,

oxazepam, lorazepam, temazepam, and morphine metabolism remain unchanged in the presence of significant liver disease as these drugs are metabolized primarily via glucuronidation.^{83,84} Oral administration of drugs with a high extraction ratio (high first-pass metabolism) are more likely to yield higher than intended serum levels of the active compound in patients with cirrhosis and should be used carefully.⁸²

In clinical practice, two common drug classes that may be used in patients with liver disease include and the HMG-CoA reductase inhibitors, collectively known as “statins,” and nonsteroidal anti-inflammatory drugs (NSAIDs).

Although clinically significant liver injury from statins is relatively rare, asymptomatic elevations in liver enzymes are common.⁸⁵ Despite animal studies suggesting that statins may cause significant liver injury, it does not appear that statins are a predictable cause of hepatocellular necrosis in humans. While hyperlipidemic patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity compared to hyperlipidemic patients with normal transaminases,⁸⁶ the safety of statins in patients with cirrhosis has not been systematically studied. The decision to use these agents in patients with cirrhosis should follow careful consideration of the potential benefits of therapy versus the risk of hepatotoxicity and myopathy. It is generally believed that the risk of statin-associated myopathy increases with increasing serum drug concentration.⁸⁷ Patients with decompensated cirrhosis are likely to have higher serum levels of statins because the activity of CYP3A is likely to be reduced. However, there are no reports of increased rhabdomyolysis with the use of statins in patients with cirrhosis. Pravastatin is not metabolized by the CYP system and may be associated with a lower risk of hepatotoxicity.⁸⁸

NSAID-related hepatotoxicity is usually a result of idiosyncratic reactions rather than intrinsic toxicity of the agent, and thus is usually unpredictable. Among the NSAIDs, diclofenac and sulindac are two agents that are more likely to cause hepatotoxicity^{89,90} and should probably be avoided in patients with liver disease. NSAIDs as a group should be avoided in patients with ascites or a history of ascites. Inhibition of endogenous prostaglandin production leads to impairment of renal hemodynamics and causes sodium retention and edema, even in patients with well-compensated cirrhosis.^{91,92} For these reasons, acetaminophen is preferred over NSAIDs for the treatment of pain in patients with cirrhosis. A recent small study suggests that short-term administration of the selective cyclooxygenase (COX)-2 inhibitor celecoxib (Celebrex, Pfizer) does not impair renal function or response to furosemide in subjects with decompensated cirrhosis, ascites, and preserved renal function.⁹³ Further studies are

needed to confirm the long-term safety of selective COX-2 inhibitors in cirrhosis; currently their use is not recommended in the subset of patients with advanced cirrhosis, ascites, or renal insufficiency.

Screening and Managing Non-Liver Diseases in Patients With Cirrhosis

Many patients with cirrhosis see the gastroenterologist as their sole healthcare provider. Office visits are often centered on the liver disease and other aspects of the patient's healthcare may be overlooked. Age over 50 or a family history–related risk for colon carcinoma should prompt appropriate colon cancer screening. For women, periodic mammograms and pelvic examinations should be completed as recommended by current guidelines. Monitoring for prostate cancer in at-risk men should also be undertaken. Diabetes is a frequent complication of cirrhosis,⁹⁴ and monitoring for the development of glucose intolerance is recommended by measuring fasting blood glucose every 6 months.

Nutrition counseling for patients with cirrhosis is important. Muscle wasting is common in patients with cirrhosis and can be delayed or ameliorated with adequate protein intake and exercise. Patients with cirrhosis should receive a minimum of 1.5 g/kg per day of protein.⁹⁵ Protein should not be restricted in the absence of clinical signs of hepatic encephalopathy. Asymptomatic elevation of serum ammonia levels is not clinically significant and should not trigger changes in the management of the patient. Serum ammonia levels should not be routinely checked in the stable cirrhotic patient. Once encephalopathy develops, restrict protein intake below 1 mg/kg per day only if symptoms are not controlled with appropriate therapy.⁹⁶

When to Refer for Liver Transplantation

Most patients with cirrhosis do not need to be referred to a liver transplant center once cirrhosis is diagnosed. Initial referral to a transplant center should be considered once the patient reaches a MELD score of 12–15, or develops a life-threatening complication of cirrhosis (such as variceal bleeding or spontaneous bacterial peritonitis). Patients with early HCC (1 lesion >2 cm but <5 cm in diameter, or up to 3 lesions not more than 3 cm each) automatically receive a MELD score of 24 regardless of the degree of hepatic decompensation and are thus prioritized for liver transplantation.⁹⁷ Patients are usually transplanted after reaching a MELD score of 20 or higher.

Only subjects suitable for liver transplantation should be referred. Patients with active alcohol or illicit drug use during the prior 6 months, those without strong family and social support, and those who are not compliant

with office visits and medications generally are not good transplant candidates. Patients that have other major illnesses such as cardiac, renal, or pulmonary diseases or extrahepatic malignancy may not be ideal candidates for liver transplantation and will require careful evaluation before listing. Severe obesity, defined as a body mass index greater than 35, is associated with a significantly worse chance for survival after transplantation.²⁸ Thus, it is important for these patients to lose weight prior to liver transplantation.

Summary

Many patients with compensated cirrhosis have a relatively long life expectancy. Patient education, appropriate surveillance and preventive strategies, and regular monitoring of their condition can improve the patient's quality of life and delay or prevent many of the serious complications associated with cirrhosis.

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