Preventive Strategies in Chronic Liver Disease: Part II. Cirrhosis

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Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The modified Child-Pugh score, which ranks the severity of cirrhosis based on signs and liver function test results, has been shown to predict survival. Strategies have been established to prevent complications in patients with cirrhosis. Esophageal varices can be identified by endoscopy; if large varices are present, prophylactic nonselective beta blocker therapy should be administered. Alpha-fetoprotein testing and ultrasonography can be effective in screening for hepatocellular carcinoma. Vaccines should be administered to prevent secondary infections. The use of nonsteroidal anti-inflammatory drugs should be avoided, and patients should maintain a balanced diet containing 1 to 1.5 g of protein per kg per day. An extensive assessment should be performed before patients with cirrhosis undergo elective surgery. Before advanced liver decompensation occurs, patients should be referred for liver transplantation evaluation. If advanced cirrhosis is present and transplantation is not feasible, survival is between one and two years. (Am Fam Physician 2001;64:1735-40.)

A patient information handout on cirrhosis, written by Andy Wapner, medical editing clerkship student at Georgetown University Medical Center, is provided on the AFP Web site.

This is part II of a two-part article on preventive strategies in chronic liver disease. Part I, "Alcohol, Vaccines, Toxic Medications and Supplements, Diet and Exercise," appeared in the November 1 issue (Am Fam Physician 2001;64:1555-60).

Chronic liver disease generally progresses slowly from hepatitis to cirrhosis, often over 20 to 40 years. Some forms of liver disease are nonprogressive or only slowly progressive. Other, more severe forms are associated with scarring and architectural disorganization, which, if advanced, lead to cirrhosis.[1]

Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[2] At the cirrhotic stage, liver disease is considered irreversible. Cirrhosis is a relatively frequent cause of death in the United States (8.8 deaths per 100,000 population per year).[3] When liver decompensation occurs and if the patient is a suitable candidate, liver transplantation is the only treatment that extends life.

Various scoring systems are used to assess the severity of disease and determine the prognosis in patients with cirrhosis. The modified Child-Pugh score, which ranks disease severity on the basis of signs and the findings of liver function tests, has been shown to predict survival[1] *(Table 1)*. Based on the total point score, patients are categorized into one of three stages. Those with Child class A cirrhosis may survive as long as 15 to 20 years, whereas those with Child class C cirrhosis may survive only one to three years.

In patients with cirrhosis, potential complications include variceal gastrointestinal bleeding, coagulopathy, ascites, hepatic encephalopathy and hepatocellular carcinoma. Strategies have been established to prevent some of these complications or to detect them at an early stage. Preventive strategies can maximize the time to transplantation or death by slowing further liver damage and alleviating comorbid conditions. This article discusses preventive care strategies that have been shown to be effective or to have a scientific rationale in patients with cirrhosis.

Preventive Strategies

VARICES AND BLEEDING

When the portal-to-systemic venous pressure gradient is persistently higher than 12 mm Hg, collateral vessels form at the junctures of the portal and systemic venous systems. When these vessels form in the distal esophagus and stomach, the usually small rudimentary left gastric vein dilates and varices develop.

On endoscopic examination, varices are found in 60 percent of patients with cirrhosis. Variceal bleeding as a result of portal hypertension is a serious complication of cirrhosis.

TABLE 1
Modified Child-Pugh Score

	*Points assigned to laboratory values and signs**		
Parameters	*1*	*2*	*3*
Laboratory value			
Total serum bilirubin level	<2 mg per dL (34 µmol per L)	2 to 3 mg per dL (34 to 51 µmol per L)	>3 mg per dL
Serum albumin level	>3.5 g per dL (35 g per L)	2.8 to 3.5 g per dL (28 to 35 g per L)	<2.8 g per dL
International Normalized Ratio	< 1.70	1.71 to 2.20	>2.20
Signs			
Ascites	None	Controlled medically	Poorly controlled
Encephalopathy	None	Controlled medically	Poorly controlled

**—Based on total points, a patient with cirrhosis is assigned to one of three classes: Child class A = 5 to 6 points; Child class B = 7 to 9 points; Child class C = 10 to 15 points.*

In patients with large varices, the risk of bleeding is about 40 to 45 percent each year. With each incidence of bleeding, the risk of death can be as high as 50 percent.[4]

Recently, the American College of Gastroenterology (ACG)[5] recommended endoscopic screening to detect varices in patients with cirrhosis and no previous variceal hemorrhage. The ACG further recommended beta-blocker therapy for patients found to have large varices. Endoscopic criteria have been defined to predict which patients are at high risk for variceal bleeding. These criteria include large varices and varices with red wale markings. A high Child score also indicates an increased risk for variceal bleeding.[6]

Nonselective beta blockers are recommended for primary prophylaxis against variceal bleeding. Several randomized trials have shown that beta blockers such as propranolol and nadolol can reduce the risk of initial variceal bleeding from about 45 percent to 22 percent.[7] In four randomized trials, endoscopically proven esophageal varices were treated with propranolol or nadolol in dosages designed to reduce the heart rate by 20 to 25 percent from the basal rate.[8] The usual starting dosage for propranolol is 10 mg three times daily. Nadolol is generally initiated in a dosage of 20 mg once daily.

The combination of serum alpha-fetoprotein testing and liver ultrasonography is effective in detecting early hepatocellular carcinoma.

Isosorbide mononitrate has been shown to be effective as second-line therapy in patients who have side effects from beta blockers or in whom beta blocker therapy is contraindicated.[9] Isosorbide mononitrate is given in a dosage of 20 mg twice daily.

Medication prophylaxis is unnecessary in patients with no varices or only small varices that do not have red wale markings. If initial endoscopy shows no varices, the examination should be repeated in one to two years to assess the risk of bleeding.

Patients who have had one episode of bleeding should receive secondary prophylaxis with esophageal banding or sclerotherapy to obliterate the varices. They should also be treated with beta blockers and undergo surveillance endoscopy at regular intervals.

SCREENING FOR HEPATOCELLULAR CARCINOMA

Most patients with cirrhosis are at high risk for hepatocellular carcinoma, with one study showing a cumulative 22.9-fold increased risk after three and one-half years.[10] In the United States, hepatitis C is the most common cause of cirrhosis and, once cirrhosis has developed, hepatocellular carcinoma.

Hepatocellular carcinoma is a leading cause of death in patients with cirrhosis.[10] Patients with advanced-stage cancer have a three-year survival rate of 17 percent.[11] When hepatocellular carcinoma is not diagnosed until patients have symptoms, mean survival is often less than four months.[12] However, tumor resection or liver transplantation has been found to prolong survival in patients with asymptomatic small tumors (smaller than 5 cm in greatest diameter).[12] An 85 percent

five-year survival has been reported in patients with liver tumors smaller than 2 cm in size.[13]

All patients with cirrhosis should be screened for hepatocellular carcinoma on a regular basis. Two screening techniques have been suggested: serum alpha-fetoprotein testing and liver ultrasonography.[13] For the detection of hepatocellular carcinoma, alpha-fetoprotein testing has a sensitivity of 64 percent and a specificity of 91 percent when the serum alpha-fetoprotein level is higher than 20 ng per mL (20 mg per L).[14] Liver ultrasound examination has a sensitivity of 59 to 74 percent and a specificity of 94 percent.[13] Screening is imperfect when serum alpha-fetoprotein testing and liver ultrasonography are used alone. Used in combination, however, these methods are effective in detecting early hepatocellular carcinoma.

The optimal frequency of screening is not known. In a recent study,[10] initial alpha-fetoprotein testing detected hepatocellular carcinoma in 22 of 27 patients with the malignancy, and follow-up testing detected cancer in the other five patients. These data suggest that alpha-fetoprotein testing should be performed every six months. The recommended frequency of ultrasound screening is every six months to one year.[10]

As a screening test, ultrasonography is more cost-effective than computed tomographic (CT) scanning. If a patient with cirrhosis has an elevated alpha-fetoprotein level or an abnormal ultrasound examination, triphasic CT scanning (capture of arterial contrast images) should be performed. Given the rich arterial supply of hepatocellular carcinoma, tumors smaller than 2 cm in size can be detected on a triphasic CT scan.[15]

VACCINATIONS

No vaccine for hepatitis C is currently available. Hepatitis A and B vaccines should be given to all patients with cirrhosis who are not shown to be immune to the diseases. Hepatitis B vaccine has much lower immunogenicity in patients with cirrhosis and portal hypertension than in those with earlier stages of chronic liver disease.[16]

Patients with cirrhosis should be given a single dose of polyvalent pneumococcal vaccine as protection against infections such as peritonitis and pneumonia. *Streptococcus pneumoniae* is the third most common isolate from spontaneous bacterial peritonitis.[17]

Mortality from influenza is increased in patients with cirrhosis. Therefore, these patients should receive annual injections of influenza vaccine.[18]

AVOIDANCE OF MEDICATION TOXICITY

Prevention of drug toxicity is essential in patients with cirrhosis. Tables listing selected potentially hepatotoxic medications and others substances are provided in part I of this two-part article.

In patients who have cirrhosis with related coagulopathy and portal hypertension, nonsteroidal anti-inflammatory drugs (NSAIDs) make bleeding more likely because they inhibit platelet function and can cause gastrointestinal ulceration.[19] In patients with portal hypertension, renal blood flow depends significantly on prostaglandins. NSAIDs inhibit prostaglandins, which can lead to decreased renal blood flow because of afferent arteriolar vasoconstriction. As a result, acute renal failure can occur in patients who have cirrhosis. Because of their toxicity, NSAIDs should be avoided in patients with cirrhosis.[20]

Compared with other NSAIDs, the newer selective cyclooxygenase-2 (COX-2) inhibitors cause less gastrointestinal mucosal injury. However, there is no evidence that use of COX-2 inhibitors decreases the risk of hepatic and renal injury.

The effects of acetaminophen on the liver are dose dependent. Acetaminophen can be used safely in a dosage of 500 mg four times daily (2 g per day). However, hepatotoxicity has been reported with acetaminophen dosages of less than 4 g of per day, usually in association with alcohol ingestion or starvation.[21]

DIET

Patients with cirrhosis tend to retain salt. Cirrhosis can lead to portal hypertension, low albumin levels and increased sodium reten-

Patients with cirrhosis should maintain a balanced diet containing 1 to 1.5 g of protein per kg per day.

tion, which can culminate in the development of ascites.

Diet is the first and most important intervention in patients with cirrhosis. In the earliest stages of cirrhosis, urinary sodium excretion is plentiful, and a negative salt balance can be achieved by restricting sodium intake to 2 g per day. In one series[22] of patients referred for a LeVeen peritoneovenous shunt and requiring frequent paracentesis, a careful history revealed that several patients were eating massive quantities of dill pickles (more than 12 g of sodium per day). After these patients stopped consuming pickles, they required no further paracentesis.

Once ascites develops, patients with cirrhosis must continue to follow a sodium-restricted diet. Frequently, these patients also require diuresis, with spironolactone (Aldactone) as first-line therapy and occasional use of a supplemental loop diuretic.

The liver is the metabolic center for all nutrients. Liver disease can interfere with metabolism in the organ and, thus, can have a negative impact on nutritional status. Because of hepatic damage, patients with cirrhosis can develop marked malnutrition, especially muscle-wasting protein malnutrition. Therefore, patients with cirrhosis should maintain a balanced diet containing 1 to 1.5 g of protein per kg per day. However, patients with advanced cirrhosis can develop encephalopathy if they consistently consume large portions of protein at one time. These patients should eat small but more frequent servings to maintain a diet of 1 g of protein per kg per day.

Ascites and Spontaneous Bacterial Peritonitis

In patients with cirrhosis, the development of ascites is the most common form of clinical decompensation and carries a poor prognosis. Complications, including spontaneous bacterial peritonitis and renal insufficiency, further worsen the prognosis.

Evaluation for liver transplantation should be considered in all patients who develop ascites. Patients with new-onset ascites or clinical deterioration should undergo paracentesis. In portal hypertension, the albumin level in serum minus the albumin level in ascitic fluid (gradient) is more then 1.1 mg per dL. When this gradient is less than 1.1, etiologies other than portal hypertension should be considered, most commonly peritoneal carcinomatosis or abdominal tuberculosis.[23]

Spontaneous bacterial peritonitis is diagnosed when the neutrophil count in ascitic fluid is greater then 250 cells per mm^3 or cultures of ascitic fluid are positive.[23] The diagnosis of spontaneous bacterial peritonitis heralds advanced liver disease.

One randomized, placebo-controlled trial[24] showed that norfloxacin decreased the risk of a second episode of spontaneous bacterial peritonitis from 68 percent to 20 percent. A recent meta-analysis[25] of 534 patients with ascites and gastrointestinal bleeding found that short-term antibiotic prophylaxis significantly increased the mean percentage of patients who were free of infection and also significantly increased short-term survival.

Enthusiasm for antibiotic prophylaxis should be tempered by the possibility of the development of resistant bacterial strains with long-term use. Antibiotic resistance is particularly alarming in patients being considered for liver transplantation. Given the conflicting variables, a preventive strategy cannot be definitely recommended. If used, antibiotic prophylaxis should be employed only in selected patients, and its duration should be limited to six months to avoid the development of antibiotic resistance.

Risk of Complications with Surgery

When patients with cirrhosis undergo elective or emergency surgery, they are at significant risk for postoperative complications leading to death. The most accurate predictor of outcome is the preoperative Child class *(Table 1)*. One study[26] reported a mortality rate

of 10 percent in patients with Child class A cirrhosis, compared with 30 percent in patients in Child class B cirrhosis and 82 percent in those in Child class C disease.

Factors associated with perioperative complications and mortality include male gender, a high modified Child-Pugh score, the presence of ascites, a diagnosis of cirrhosis other than primary biliary cirrhosis (especially cryptogenic cirrhosis), an elevated creatinine concentration and the occurrence of preoperative upper gastrointestinal bleeding.[27]

Because of the increased risk of complications or death, careful consideration should be given before surgery is performed in patients with cirrhosis. It is mandatory to perform a preoperative assessment with calculation of the Child class, assessment of the risk of bleeding and weighing of risks and benefits.

Liver Transplantation

Orthotopic liver transplantation is the definitive treatment for a variety of irreversible problems related to chronic liver disease. At present, about 4,000 liver transplant procedures are performed at 100 medical centers annually.[28] There are currently about 18,000 potential candidates for liver transplantation, and this number continues to increase each year.[29] In many medical centers where liver transplantation is performed, the one-year survival rate is about 85 percent, and the five-year survival is approximately 75 percent.[29]

Rather than waiting for signs of advanced liver decompensation, physicians should refer patients for liver transplantation evaluation when early signs occur. In many medical centers, the average waiting time for a liver is between two and three years. An evaluation for liver transplantation should be performed in all patients with Child class B cirrhosis and all patients with ascites.

Measures that can be effective in preventing liver decompensation in patients with cirrhosis are summarized in *Table 2.*

Palliative Care

Many patients with advanced cirrhosis are not suitable candidates for liver transplantation for a variety of reasons, including the presence of cancer, active alcohol abuse, chronic infection and other medical problems (e.g., advanced cardiopulmonary disease). Patients with multifocal, bilobar, large hepatocellular carcinomas larger than 5 cm in size do not qualify for liver transplantation.

Patients with advanced cirrhosis who are not candidates for liver transplantation generally survive only one to two years. They develop ascites, irreversible coagulopathy, encephalopathy and spur-cell anemia. In these patients, supportive and comfort care is most prudent. As death approaches, hospice care is often appropriate.

It is imperative to discuss a living will and advance directives with patients who have terminal cirrhosis. Discussing these patients' wishes before end-of-life care is needed can prevent an unwanted, painful and futile course. Good communication concerning prognosis and comfort-care measures can allow patients with end-stage liver disease to die with dignity, often at home with their family.

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TABLE 2
Preventive Measures in Cirrhosis

Complete abstinence from alcohol
Vaccination against hepatitis A and hepatitis B (if the patient is not already immune); single dose of polyvalent pneumococcal vaccine; annual (autumn) influenza vaccine
Avoidance of hepatotoxic medications, especially nonsteroidal anti-inflammatory drugs*
Avoidance of iron supplements unless iron deficiency anemia is present; multivitamins without iron should be used
Low-fat, "heart-smart" diet
Endoscopy once yearly to screen for and evaluate esophageal varices
Alpha-fetoprotein testing every six months and ultrasonography once yearly to detect early hepatocellular carcinoma
Avoidance of elective surgery once signs of liver decompensation develop
Referral for liver transplantation evaluation in patients with Child class B cirrhosis and patients with ascites

**—The safest choice is acetaminophen in a dosage of less than 2 g per day.*

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