

# The Liver Transplant Patient

## Part I: Managing Adults with Cirrhosis

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**O**rthotopic liver transplantation is a surgical procedure in which the diseased native liver is removed and replaced with all or part of a healthy liver obtained from a deceased or living human donor. The first liver transplantation was performed in 1963. Initially, overall outcomes were poor and liver transplantation remained experimental. Following advances in immunosuppression in the late 1970s, survival improved dramatically, and in the mid-1980s, liver transplantation began to move into the mainstream of clinical practice. Liver transplantation today is the established standard of care for many patients with end-stage liver disease. In 2005, more than 6400 liver transplants were performed in the United States at 119 sites.<sup>1</sup>

Transplantation is carried out in tertiary centers by teams of specialists experienced in caring for patients with advanced liver disease, performing transplant surgery, and managing posttransplant immunosuppression. However, every physician can expect to encounter liver transplant patients in clinical practice and should be familiar with some basic aspects of evaluation and management. This article is part 1 of a 2-part series on medical care of adults before and after liver transplantation. Part 1 discusses the primary care physician's role of identifying patients with liver disease who may require liver transplantation and optimizing management of liver disease while the patient awaits transplantation. Part 2, to be published in the April 2007 issue of *Hospital Physician*, will review liver transplantation and discuss common health problems encountered in the posttransplant patient.

### INDICATIONS FOR LIVER TRANSPLANTATION

Most liver transplants are performed for cirrhosis of the liver. Cirrhosis and its complications (eg, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, variceal hemorrhage, and hepatocellular carcinoma [HCC]) cause approximately

### TAKE HOME POINTS

- Cirrhosis often presents insidiously with subtle laboratory abnormalities, such as thrombocytopenia or mild elevation of aspartate aminotransferase. Diagnosis is supported by imaging studies and confirmed by percutaneous liver biopsy.
- Cirrhosis is the final common pathway of many types of liver injury. Treatment directed at the underlying etiology may arrest disease progression, stabilize liver function, and eliminate or delay the need for liver transplantation.
- Optimal medical management of cirrhosis, including substance abuse treatment, control of ascites, prevention of variceal bleeding, control of encephalopathy, regular surveillance imaging for hepatocellular carcinoma, infection control and immunization, and attention to nutrition and general health, improves the chances that the patient will survive to receive a liver transplant.
- Transplant evaluation requires a thorough assessment of medical, surgical, psychological, and social factors that may contribute to risk of a poor outcome.
- The Model for End-stage Liver Disease (MELD) score predicts risk of pretransplant death in cirrhotic patients and is the basis for assigning liver transplant priority in the United States.

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40,000 deaths annually in the United States.<sup>2</sup> Liver transplantation also may be indicated in other medical conditions, such as fulminant hepatic failure, otherwise unresectable hepatic cancers, certain inborn errors of metabolism, intractable biliary sepsis, noncirrhotic portal hypertension, or polycystic liver disease. With the exception of fulminant hepatic failure, these conditions represent only a small fraction of all transplants. Approximately 10% of US liver transplant recipients are children, whose care presents special challenges. (Evaluation and management of children with liver disease is beyond the scope of this review.)

## DIAGNOSIS OF CIRRHOSIS

### Laboratory and Imaging Studies

Hepatic cirrhosis usually develops insidiously over many years in response to chronic hepatic injury. Elevated liver cytosolic enzymes (alanine transaminase [ALT], aspartate transaminase [AST]) suggest liver injury but do not indicate liver disease severity, and ALT and AST levels are often normal in patients with cirrhosis. Several routine laboratory findings are helpful indicators of early cirrhosis, including the platelet count, AST/ALT ratio, and international normalized ratio (INR). Indices that incorporate these parameters can reliably detect the presence of cirrhosis in many patients with chronic hepatitis C.<sup>3,4</sup>

Mild to moderate thrombocytopenia, caused by portal hypertension with splenic congestion and platelet sequestration, is encountered in over half of all patients with cirrhosis.<sup>5</sup> Thrombocytopenia often develops at a time when liver disease may be unrecognized, and it may be misdiagnosed as idiopathic thrombocytopenic purpura. The AST/ALT ratio normally averages around 0.7 in patients without liver disease, but it rises with progressive fibrosis in hepatitis C<sup>6</sup> or nonalcoholic steatohepatitis.<sup>7</sup> An AST/ALT ratio greater than 1 is 60% to 80% specific for cirrhosis in patients with chronic hepatitis C, and specificity improves at higher values.<sup>6–8</sup> Because the AST/ALT ratio also may be elevated by alcohol abuse and may fluctuate between determinations (especially in patients with transaminase values in the normal range), it can be misleading if viewed without considering other indicators of disease.<sup>8,9</sup> Global measures of liver function (eg, serum levels of bilirubin or albumin or INR) deteriorate as cirrhosis progresses and are relatively specific; however, these tests are usually normal in early cirrhosis.

Imaging studies, such as liver ultrasound or computed tomography, are helpful in demonstrating anatomic findings suggestive of cirrhosis and should be ordered if cirrhosis is suspected. Features suggestive of cirrhosis

include increased irregularity of the hepatic parenchyma, nodularity of the liver surface, overall reduction in liver size with enlargement of the caudate lobe and left lobe relative to the right lobe, increased portal vein diameter with reduced flow velocity, presence of varices, recanalization of the umbilical vein, ascites, and splenomegaly.<sup>9,10</sup> When present, radiographic features of cirrhosis are highly specific but are relatively insensitive for detecting cirrhosis in early stages.

### Liver Biopsy

The current gold standard for detecting advanced fibrosis and cirrhosis is liver biopsy. Liver biopsy often is unnecessary when cirrhosis is clinically evident, but biopsy findings can be useful in 3 ways. First, findings on the biopsy may provide important clues to identify or exclude particular etiologies of liver disease (eg, hepatocellular iron deposition indicative of hemochromatosis, cytosolic inclusions indicative of  $\alpha_1$ -antitrypsin deficiency). Second, the biopsy may be used semiquantitatively to assess the severity of ongoing inflammation and necrosis (disease grade). Finally, the biopsy shows the extent of fibrosis (disease stage) and can detect cirrhosis that is otherwise not apparent on clinical evaluation. Liver biopsy is subject to sampling error and may miss cirrhosis in some cases. (The role of liver biopsy in evaluation and management of liver disease is summarized in a recent review.<sup>11</sup>)

Percutaneous liver biopsies involve low risk and are routinely performed by gastroenterologists or invasive radiologists on an outpatient basis. Liver biopsy can also be obtained during conventional or laparoscopic surgery. In patients with thrombocytopenia, coagulopathy, or ascites, risk of hemorrhage can be reduced by performing liver biopsy via the transjugular route. Transjugular liver biopsy requires hepatic venous cannulation by an angiographer under fluoroscopic guidance. This approach also permits measurement of hepatic venous free and wedged pressures to determine the hepatic venous pressure gradient (HVPG), which usually reflects the severity of portal hypertension. Changes in HVPG may be a useful measure of response to treatment in some settings.<sup>12,13</sup>

### IDENTIFYING AND TREATING THE CAUSE OF CIRRHOSIS

In addition to clinical evaluation, imaging, and liver biopsy, various laboratory tests are useful in establishing the etiology of liver disease (**Table 1**). For many liver diseases, such as alcoholic liver disease, hepatitis B and C, autoimmune hepatitis, hemochromatosis, and Wilson's disease, treatments that target the specific etiology have been shown to arrest progression and prolong life and

**Table 1.** Selected Causes of Cirrhosis in Adults with Clinical and Biopsy Features

Cause	Clinical Diagnosis	Liver Biopsy
Alcoholic hepatitis	History of alcohol abuse	Fat, perivenular injury, ballooning degeneration, neutrophils, Mallory's hyaline
Nonalcoholic steatohepatitis	Metabolic syndrome (obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia)	Fat, neutrophils, necrosis, and fibrosis
Hepatitis B	HBsAg, HBV DNA	Chronic hepatitis, ground-glass hepatocytes
Hepatitis C	Anti-HCV ELISA, HCV RNA	Chronic periportal and lobular hepatitis, lymphoid aggregates, fat
Hemochromatosis	Ferritin, transferrin saturation, <i>HFE</i> genotype	Hepatocellular iron deposition with hemosiderin granules
$\alpha_1$ -Antitrypsin deficiency	$\alpha_1$ -Antitrypsin level and phenotype	PAS-positive inclusions in hepatocytes
Wilson's disease	Ceruloplasmin, urine copper	Increased tissue copper
Autoimmune hepatitis	ANA, anti-smooth muscle antibody, or anti-liver/kidney microsomal antibodies; elevated IgG	Interface hepatitis, plasma cells, rosette formation
Primary biliary cirrhosis	Anti-mitochondrial antibody, elevated IgM	Bile ductular destruction with mixed cellular portal inflammatory infiltrate
Primary sclerosing cholangitis	Cholangiography	Onion-skin fibrosis of medium and large bile ducts, bile ductular proliferation
Hepatic venous outflow obstruction (Budd-Chiari syndrome)	Hepatic venography	Hepatic venular congestion, sinusoidal dilatation

ANA = antinuclear antibody; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PAS = periodic acid-Schiff.

may eliminate the need for transplantation (**Table 2**).<sup>14–22</sup> In other liver diseases, such as primary biliary cirrhosis, primary sclerosing cholangitis, Budd-Chiari syndrome, and nonalcoholic steatohepatitis, therapies are available that may slow progression, reduce symptoms, or prevent complications (**Table 2**). It is common for patients to have multiple etiologies for their liver disease; thus, even when 1 cause of liver disease is apparent, other treatable causes must be excluded. In about 5% of cases of cirrhosis leading to transplantation, no etiology can be identified (ie, cryptogenic cirrhosis<sup>23</sup>).

### ACHIEVING AND MAINTAINING SOBRIETY

Alcohol, drug, and tobacco abuse are common in patients with cirrhosis. Regardless of the cause of liver disease, moderate to heavy use of alcohol can be expected to accelerate liver injury. For example, in patients with hepatitis C, concurrent heavy use of alcohol increases the likelihood of developing cirrhosis by two- to fivefold compared with no alcohol use.<sup>24</sup> Addictive behavior is also a major barrier to transplantation and needs to be addressed. Although drugs of abuse such as heroin, cocaine, and methamphetamine have little direct effect on long-term liver function, patients who continue to abuse these substances generally are poorly compliant with medical regimens and have poor outcomes after transplantation.<sup>25</sup> Abstinence from tobacco

**Table 2.** Causes of Cirrhosis and Recommended Treatments

Cause	Treatment
Alcoholic hepatitis	Abstinence from alcohol
Hepatitis B	Lamivudine, adefovir, entecavir, interferon alfa <sup>14</sup>
Hepatitis C	Interferon alfa, ribavirin <sup>15</sup>
Autoimmune hepatitis	Glucocorticoids, azathioprine <sup>16</sup>
Hemochromatosis	Phlebotomy <sup>17</sup>
Wilson's disease	D-Penicillamine, zinc, trientine <sup>18</sup>
$\alpha_1$ -Antitrypsin deficiency	None
Primary biliary cirrhosis	Ursodiol <sup>19</sup>
Primary sclerosing cholangitis	Stenting of dominant strictures
Hepatic venous outflow obstruction (Budd-Chiari syndrome)	Anticoagulants, portosystemic shunting <sup>20</sup>
Nonalcoholic steatohepatitis	Weight loss, <sup>21</sup> insulin-sensitizing agents <sup>22</sup>

should also be strongly encouraged, as tobacco-related health problems, including cancer, atherosclerosis, and lung disease, are major causes of morbidity and mortality after transplantation.<sup>26,27</sup>

### MANAGING COMPLICATIONS OF CIRRHOSIS

A mnemonic summarizing 10 key considerations in comprehensive management of the cirrhotic patient is

**Table 3.** PORTAL VEIN: A Mnemonic Summarizing 10 Key Considerations in Management of the Cirrhotic Patient

<b>P</b>	Presence and prognosis: recognizing cirrhosis and assessing severity
<b>O</b>	Origin: identifying and treating the cause
<b>R</b>	Rehabilitation: managing substance abuse
<b>T</b>	Transplant triage: assessing indications and contraindications
<b>A</b>	Ascites: evaluation and treatment
<b>L</b>	Lifestyle, nutrition, and general health
<b>V</b>	Variceal bleeding prevention
<b>E</b>	Encephalopathy: recognition and management
<b>I</b>	Infection prevention: immunization and antibiotic prophylaxis
<b>N</b>	Neoplasia: surveillance for hepatocellular carcinoma

provided in **Table 3**.<sup>28</sup> General aspects of cirrhosis management are discussed below.

### Ascites and Edema

Cirrhotic ascites is characterized by a serum-ascites albumin gradient greater than 1.1 g/dL, usually accompanied by very low levels of albumin and total protein level less than 2.5 g/dL.<sup>29</sup> Initial management of ascites consists of salt restriction and a distal tubular diuretic (most commonly spironolactone), which is potentiated by administration of a loop diuretic (eg, furosemide) at the lowest effective doses. A diagnostic paracentesis is recommended at initial presentation of ascites.<sup>30</sup> Total paracentesis may be useful in initial control of ascites and in long-term care of patients who are refractory to diuretic therapy. However, total paracentesis can lead to transient hypotension and prerenal azotemia (postparacentesis circulatory dysfunction), and some experts favor infusion of 6 to 8 g of albumin per liter of ascites removed in order to prevent these effects.<sup>30</sup> Albumin infusion is costly and has not been shown to alter mortality, and its use remains controversial.<sup>30</sup> In selected patients, refractory ascites may improve or resolve following transjugular intrahepatic portosystemic shunting, but this procedure can increase the severity of hepatic encephalopathy and does not appear to prolong survival.<sup>31,32</sup>

### Hepatic Encephalopathy

Portosystemic shunting of ammonia and other toxins produced by intestinal bacteria leads to hepatic encephalopathy. Hepatic encephalopathy is characterized by sleep disturbance, difficulty in concentrating, and lethargy, which progresses to confusion and, in some cases, coma.<sup>33,34</sup> Acute exacerbations can be precipitated by a variety of factors, including dehydration,

electrolyte derangements, infection, gastrointestinal bleeding, sedative medications, and constipation. The mainstay of treatment is lactulose, a nonabsorbable carbohydrate that is fermented in the colon, which acidifies stool and produces an osmotic purge. Dosage is titrated to produce 2 to 3 loose stools per day. Branched-chain amino acid supplements or antibiotics (eg, neomycin, metronidazole, rifaximin) may also help in controlling encephalopathy symptoms but may confer additional cost or toxicity.<sup>33,34</sup> Chronic dietary protein restriction should be avoided, as protein malnutrition worsens liver function and increases susceptibility to infection.

### Variceal Hemorrhage

Patients with cirrhosis should undergo periodic endoscopy (every 2–3 yr) to monitor for varices.<sup>35</sup> In patients with large varices, prophylactic administration of nonselective  $\beta$ -blockers (propranolol or nadolol) may reduce portal pressure and has been shown to reduce likelihood of initial variceal bleeding as well as rebleeding.<sup>36,37</sup> When bleeding occurs, endoscopic band ligation usually controls acute hemorrhage. Thereafter, band ligation is repeated periodically until varices are completely ablated. Endoscopic band ligation generally is preferred over sclerotherapy because it is associated with fewer complications.<sup>38</sup> Serial band ligation and  $\beta$ -blockers are sufficient to prevent recurrent bleeding in most cases, but when these measures fail, transjugular intrahepatic portosystemic shunting usually normalizes portal pressure and prevents further bleeding.<sup>39,40</sup>

### Hepatocellular Cancer Surveillance

Cirrhosis is associated with a significant risk of primary HCC. In patients with cirrhosis caused by viral hepatitis or alcohol, the annual incidence of HCC ranges from 1% to 5% and is higher in males, with advanced age, or with ongoing liver injury.<sup>41</sup> Because some liver cancers may be curable if detected early, periodic surveillance of cirrhotic patients with liver imaging and measurement of serum alpha-fetoprotein (AFP) is generally recommended.<sup>42</sup> AFP, the fetal form of albumin, is elevated in about two thirds of patients with HCC at the time of diagnosis, but mild elevations also are encountered in many cirrhotic patients in the absence of cancer. A variant of AFP, termed AFP-L3, is more specific for HCC and is a marker of more aggressive tumors, but its role in surveillance is still unclear.<sup>43</sup> There is no consensus regarding the ideal method or interval of surveillance,<sup>44</sup> and surveillance has not yet been proven to reduce mortality.<sup>42,45</sup>

In our program, we measure AFP every 3 months

and perform liver imaging every 6 months (ultrasound alternating with 3-phase contrast computed tomography). In patients with elevated or rising AFP or suspicious nodules, we carry out more frequent imaging, including magnetic resonance imaging. Image-guided percutaneous needle biopsy of suspicious lesions larger than 1 cm has been recommended,<sup>46</sup> but this approach carries a small risk of needle track spread of tumor and is not a universally accepted practice at this time. Potentially curative therapies for early HCC include radiofrequency ablation, partial hepatic resection, or liver transplantation.<sup>47,48</sup> Other locoregional therapies, such as transarterial chemoembolization, may be of palliative benefit.<sup>49</sup> Patients with advanced stage HCC generally are not offered liver transplantation because of the high likelihood of posttransplant recurrence. Treatments for advanced stage HCC are largely palliative, and outcomes are poor.

### Infection

Patients with liver disease who lack protective antibodies should be immunized against hepatitis A and B.<sup>50</sup> Cirrhotic patients should be advised to avoid raw shellfish because certain marine vibrios can cause fatal septicemia. Prophylactic antibiotics with broad-spectrum gram-negative coverage, such as quinolones, are indicated acutely following variceal bleeding and chronically following spontaneous bacterial peritonitis if ascites persists; this intervention has been shown to reduce serious infections in these settings.<sup>51,52</sup>

### Respiratory Complications

Several respiratory problems are associated with cirrhosis. Patients with ascites commonly develop pleural effusions, especially on the right side, presumably because the negative intrathoracic pressure draws ascites fluid through defects in the diaphragm.<sup>53</sup> Hepatic hydrothorax can be difficult to manage if there is no response to diuretics and salt restriction. Chest tubes should be avoided because of the high rate of complications, including electrolyte depletion and infection.<sup>54</sup> Patients with cirrhosis may develop hypoxemia due to hepatopulmonary syndrome (a condition caused by intrapulmonary vasodilatation with functional shunting), which can be demonstrated with bubble echocardiography. The hypoxemia responds to oxygen and usually is corrected by liver transplantation,<sup>55</sup> and patients with this condition can receive expedited transplant priority. Cirrhotic patients may develop increased pulmonary arterial pressure, a phenomenon called portopulmonary hypertension. Portopulmonary hypertension usually can be detected by Doppler echocardiography

and is confirmed by right heart catheterization. Liver transplantation can halt or reverse portopulmonary hypertension in mild cases, but severe pulmonary hypertension unresponsive to medical therapy is associated with high perioperative mortality and poor long-term posttransplant survival.<sup>56,57</sup>

### Maintaining Nutrition and General Health

Malnutrition is common in cirrhosis, especially in alcoholics and in individuals with tense ascites. Nutrition generally improves when these problems are addressed. A diet containing adequate protein and calories with supplemental vitamins and minerals should be provided. Obese patients with cirrhosis should be encouraged to lose weight. Despite chronic fatigue, patients should be encouraged to engage in regular physical activity to prevent deconditioning. Diabetes needs to be recognized and controlled. Measures should be taken to identify osteoporosis and prevent bone loss, especially if transplantation is anticipated. Surveillance for common cancers (eg, breast, cervix, colon, prostate) should follow usual guidelines.

### Surgical Risk

Surgery may carry substantial risk in the cirrhotic patient. In a large retrospective review of 733 major operative procedures in patients with cirrhosis between 1980 and 1991, Ziser and colleagues<sup>58</sup> found that 30-day postoperative mortality was 11.6% and the perioperative complication rate was 30.1%. Both mortality and morbidity were associated with male gender, cryptogenic cirrhosis (which at that time included hepatitis C), cirrhosis severity (Child-Turcotte-Pugh [CTP] class), persistent ascites, elevated creatinine, poor functional capacity, and active infection. Surgical risk is modest if liver function is normal (CTP class A), but once hepatic function has begun to deteriorate, risk increases substantially.<sup>59</sup>

### Drug Toxicity

Nonsteroidal anti-inflammatory drugs should be avoided in patients with a history of ascites because they can precipitate deterioration of renal function as well as bleeding peptic ulcers.<sup>60</sup> Sedatives and narcotics can worsen hepatic encephalopathy and should be used sparingly, with careful adjustment of lactulose dosage to prevent constipation. Acetaminophen is safe in cirrhosis at doses up to 2.5 g/day. Drugs with known hepatotoxic potential, such as antituberculous medicines, should be used only when necessary and with close monitoring of liver function. Care must be taken to reduce the dosage of drugs that are taken up and metabolized by the liver, since cirrhosis is associated

**Table 4.** Prognostic Indices for Patients with Cirrhosis

**The Child-Turcotte-Pugh score\***

Patients are ranked in 5 categories on a scale of 1, 2, or 3, and scores are added together (lowest possible score = 5; highest possible score = 15).

	1	2	3
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Serum bilirubin (mg/dL)	< 2.0	2.0–3.0	> 3.0
INR	< 1.7	1.7–2.3	> 2.3
Ascites	Absent	Minimal or controlled with diuretics	At least moderate despite diuretics
Encephalopathy	Absent	Grade 1–2	Grade 3–4

Class A = 5–6 points

Class B = 7–9 points

Class C = 10–15 points

**The MELD score** is calculated as follows:

$$\text{MELD} = 6.43 + 11.20 \times \log_e(\text{INR}) + 9.57 \times \log_e(\text{creatinine [mg/dL]}) + 3.78 \times \log_e(\text{bilirubin [mg/dL]})^\dagger$$

INR = international normalized ratio; MELD = Model for End-stage Liver Disease.

\*The Child-Turcotte-Pugh score exists in several variations; shown here is the form that was employed in the United States by the United Network for Organ Sharing for organ allocation prior to 27 Feb 2002.

†Minimum values of 1 are assigned to bilirubin, creatinine, and INR (to avoid negative logarithmic values). A maximum value of 4 is assigned to creatinine. Creatinine value is 4 for patients receiving hemodialysis at least twice in the preceding week.

with decreased first pass clearance and delayed elimination of many drugs.<sup>61</sup>

**PROGNOSTIC INDICATORS IN CIRRHOSIS**

Patients who have never experienced a complication of cirrhosis have a good overall prognosis. For example, Fattovich et al<sup>62</sup> found that survival at 10 years was almost 80% among patients with hepatitis C, biopsy-proven cirrhosis, and well-compensated liver function. In this study, the risk of developing complications in patients with previously compensated cirrhosis was approximately 3% per year. Once a cirrhotic patient has experienced a complication or has developed significant impairment of liver function, prognosis deteriorates substantially. Following onset of ascites or encephalopathy in patients with hepatitis C, median survival is 5 years or less.<sup>63</sup>

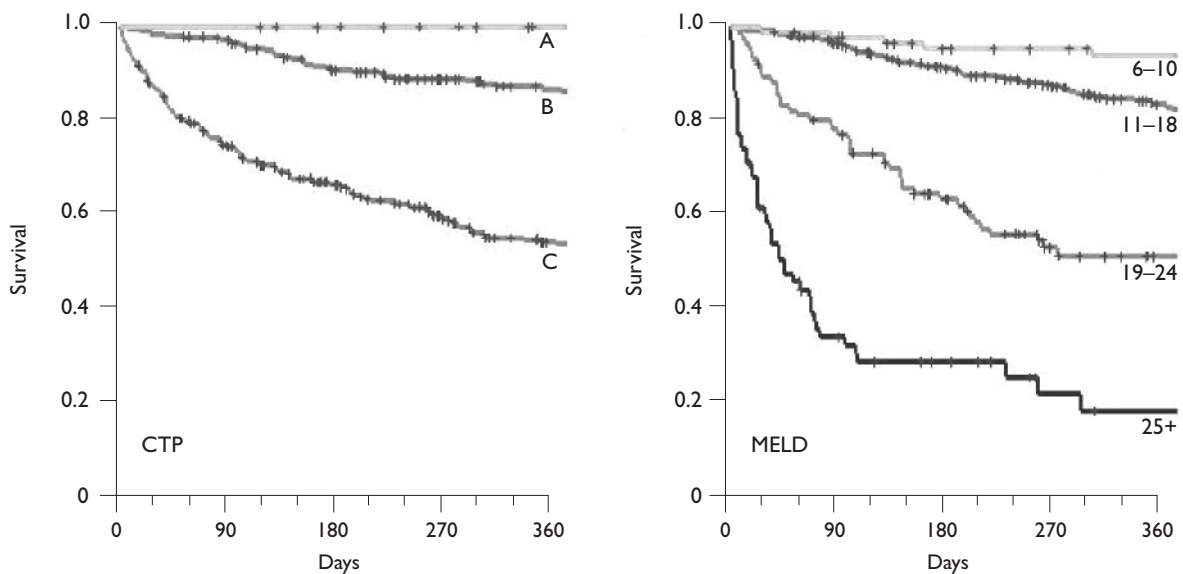
Survival is particularly poor once ascites becomes refractory to diuretic therapy, especially if accompanied

by azotemia. This phenomenon of reduced glomerular filtration with avid sodium retention and refractory ascites caused by the advanced hemodynamic derangement of cirrhosis is termed type 2 hepatorenal syndrome<sup>64,65</sup> and is associated with a median survival of less than 1 year. The terminal event in advanced cirrhosis often is characterized by rapidly progressive renal failure with hypotension (type 1 hepatorenal syndrome). Most patients with this syndrome die within weeks unless they receive a transplant.<sup>66</sup> Recent studies suggest that aggressive treatment with vasoconstrictors (eg, terlipressin, norepinephrine, or midodrine plus octreotide), volume expansion (albumin), and antibiotics can reverse type 1 hepatorenal syndrome in about half of cases if initiated early.<sup>67</sup> A hepatologist or gastroenterologist experienced in management of cirrhosis should be consulted to assist with care of these critically ill patients.

Several prognostic indices have been developed to assess mortality risk in patients with cirrhosis (**Table 4** and **Figure**). The CTP and Model for End-stage Liver Disease (MELD) scores are important for all physicians who manage cirrhosis. The CTP score has been employed for many decades and is convenient and easy to apply in the clinical setting. This score combines 2 clinical manifestations (ascites, encephalopathy) and 3 laboratory measures of liver function (albumin, INR, and bilirubin) in a semiquantitative scale. More recently, modern statistical methods of multivariate analysis have been used to derive the MELD score, which assesses mortality risk continuously using a formula based on INR, creatinine, and bilirubin. MELD is as good or better than the CTP score for assessing short-term and long-term prognosis and has the advantage that all of the components are objective laboratory measurements.<sup>68,69</sup> However, MELD underestimates mortality risk in patients with persistent ascites and low serum sodium levels.<sup>70</sup> In general, cirrhotic patients should be considered for liver transplantation if they meet any of the following criteria: (1) MELD score greater than 10; (2) CTP class B or C; (3) complications of cirrhosis, especially ascites or encephalopathy; or (4) early stage HCC (known or strongly suspected).<sup>71</sup>

**EVALUATION FOR TRANSPLANT**

Not every patient with advanced cirrhosis is a candidate for liver transplantation. Livers for transplantation are scarce, and transplantation is an exceptionally expensive and demanding treatment. Although transplant programs differ in rigorousness of selection criteria, it is generally agreed that transplantation should not be offered unless there is a reasonable likelihood of a good outcome.<sup>25,72</sup> Even in well-selected patients, 5-year



**Figure.** Pretransplant 1-year Kaplan Meier survival in cirrhotic patients as a function of Child-Turcotte-Pugh (CTP) class (left) or Model for End-stage Liver Disease (MELD) score (right). Data for 599 veterans referred for consideration of liver transplantation through the Department of Veterans Affairs, 1997–2003. (Adapted from DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004;40:802–10. Copyright © 2004, American Association for the Study of Liver Disease. Reprinted with permission of John Wiley & Sons, Inc. Heuman.)

survival following liver transplantation is no more than 80%.<sup>1,73,74</sup> Certain diseases that can recur after transplant (hepatitis C, early HCC) worsen posttransplant 5-year mortality by at least 5% to 10%. Mortality is also adversely affected in morbidly obese patients,<sup>75</sup> patients with diabetes,<sup>76</sup> and patients older than 65 years.<sup>77</sup> A variety of other comorbid conditions can worsen the expected outcome.

Once the need for transplantation has been identified, the process of transplant evaluation and triage comes down to an effort to identify potential contraindications and complicating factors and, where possible, to correct these problems.<sup>25,71,78</sup> Practice guidelines for transplant evaluation have recently been published.<sup>71</sup> An evaluation checklist employed by Department of Veterans Affairs transplant programs is shown in **Table 5**. Transplant surgery places great demands on the cardiac and respiratory systems. Although there are no fixed rules, most programs are reluctant to offer transplantation to patients with significant uncorrected coronary stenoses, severe valvular heart disease, left ventricular ejection fraction less than 40%, forced expiratory volume in 1 second less than 1.5 L, or severe pulmonary hypertension because of the high likelihood of lethal intraoperative and postoperative complications. Post-transplant immunosuppression increases susceptibility to infection. Unresolved pyogenic infections (eg, osteomyelitis) are contraindications to transplantation, and

latent tuberculosis (positive tuberculin skin test) should be eradicated prophylactically. In the past, infection with HIV was an absolute contraindication to transplantation; however, with advances in highly active antiretroviral therapy, selected patients with well-controlled, uncomplicated HIV infection and well-preserved immune function are being offered transplantation in some programs.<sup>79</sup>

Patients undergoing transplant evaluation should be screened for malignancies according to usual age- and gender-specific guidelines. In addition, patients with a history of alcohol and/or tobacco abuse merit careful evaluation to rule out lung, head and neck, or esophageal cancers. A history of extrahepatic malignancy (other than basal cell carcinoma) usually is a contraindication to transplantation unless analysis of histologic type, grade, and stage as well as treatment and posttreatment follow-up indicate very low risk of recurrence.

Psychologic and social considerations are of equal importance. Patients with addiction history must demonstrate commitment to sustained sobriety. Most programs will not list a patient for transplantation until he or she has been abstinent from alcohol and illicit drugs for at least 6 months.<sup>25</sup> Abstinence from tobacco also is important, as smoking increases the risk of posttransplant arterial thromboses,<sup>80</sup> and tobacco-related cancers and cardiovascular disease are important causes of long-term

**Table 5.** Elements of Pretransplant Evaluation: Checklist Currently Used by the Veterans Health Administration Liver Transplant Programs

**Clinical data**

- Physician's summary
- Hospital and office records
- Biopsy pathology reports (liver biopsy NOT required)
- List of current medications and allergies
- Social work evaluation
- Psychologic evaluation
- Dental evaluation
- Breast cancer screening examination and mammography (women)
- Prostate cancer screening examination and PSA (men)

**Laboratory tests**

- Blood type (ABO, Rh)
- Complete blood count
- Urinalysis
- Routine liver chemistries
- Electrolytes, creatinine, and glucose
- Coagulation studies (INR, PTT)
- 24-Hour urine creatinine clearance
- Thyroid panel
- Toxicology screens for drugs and ethanol
- Alpha-fetoprotein
- HBsAg, anti-HBc, anti-HBs
- HBV DNA (if HBsAg is positive)
- Anti-HCV
- HCV RNA and genotype (if anti-HCV is positive)
- HIV antibody
- Cytomegalovirus antibody (IgG)
- Syphilis serology

**Additional tests**

- Chest radiograph
- Electrocardiogram
- Pulmonary function tests with diffusing capacity
- Echocardiogram with assessment of pulmonary artery pressure
- Pharmacologic cardiac stress test
- Tuberculin skin test
- Doppler ultrasound of the liver
- Three-phase contrast liver imaging (CT or MRI)
- Colonoscopy (if age > 50 yr or family history)

NOTE: This represents a minimum set of studies. Additional studies often are required in high-risk patients or when abnormalities are uncovered on initial testing.

anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; anti-HCV = hepatitis C antibody; CT= computed tomography; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PTT = partial thromboplastin time.

mortality following otherwise successful liver transplantation. Major psychiatric conditions, such as schizophrenia, do not preclude transplantation provided that symptoms can be controlled with medication. A great deal of attention should be paid to ongoing compliance and social support, since patients who are unwilling or unable to comply with physician recommendations in managing general medical problems (eg, diabetes) are likely to have great difficulty and poor outcomes when faced with the demands of transplantation.

**THE TRANSPLANT LIST**

Transplant listing takes place only after a complete assessment at a transplant center and a favorable decision by the institutional transplant committee. The patient is formally listed when his/her name and key clinical data are recorded by the transplant center in the national registry maintained by the United Network for Organ Sharing (UNOS). The patient receives an official letter of notification when placed on the transplant list. If the physician or patient is uncertain about the patient's status on the transplant list, the transplant center should be contacted. Under current rules, patients may be listed at more than 1 transplant center, and patients who are turned down by 1 program may seek listing elsewhere.

Since February 2002, livers in the United States have been allocated for transplantation on a "sickest first" basis.<sup>81</sup> Priority for adults with cirrhosis currently is based on the MELD score (Table 4). Individuals with early HCC (stage II) receive supplemental MELD score points under this system in order to permit transplantation prior to cancer progression. Exceptional priority is also routinely given to patients with hepatopulmonary syndrome and those with certain rare metabolic disorders (eg, primary hyperoxaluria, familial amyloidosis). Exceptional priority can be granted in other special circumstances at the discretion of a regional or national transplant review committee. Donors and recipients are matched by major blood group (ABO). Organs are allocated first locally, then regionally, then nationally, under an algorithm that continues to evolve. Current facts, data, and policies regarding liver transplantation as well as an online MELD score calculator are available through the UNOS Web site ([www.unos.org](http://www.unos.org)).

**CONCLUSION**

End-stage liver disease represents an important and growing problem. Primary care physicians play a key role in diagnosis and care of patients with cirrhosis. A hepatology consultant can help the primary care physician establish a diagnosis, optimize treatment, prevent



or manage complications, and carry out timely transplant evaluation. Liver transplantation is a life-saving therapy for carefully selected patients with decompensated cirrhosis.

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