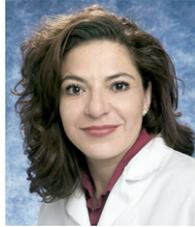


## Indications for Liver Transplantation



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**Patients should be considered for liver transplantation if they have evidence of fulminant hepatic failure, a life-threatening systemic complication of liver disease, or a liver-based metabolic defect or, more commonly, cirrhosis with complications such as hepatic encephalopathy, ascites, hepatocellular carcinoma, hepatorenal syndrome, or bleeding caused by portal hypertension. While the complications of cirrhosis can often be managed relatively effectively, they indicate a change in the natural history of the disease that should lead to consideration of liver transplantation. Referral to a liver transplant center is followed by a detailed medical evaluation to ensure that transplantation is technically feasible, medically appropriate, and in the best interest of both the patient and society. Patients approved for transplantation are placed on a national transplant list, although donor organs are allocated locally and regionally. Since 2002, priority for transplantation has been determined by the Model of End-Stage Liver Disease (MELD) score, which provides donor organs to listed patients with the highest estimated short-term mortality.**

Simply stated, the major indications for liver transplantation are irreversible hepatic failure or liver cancer. These indications are similar regardless of the etiology of the liver disease. The complex process of deciding who is a candidate for transplantation is based on the realities of rationing a limited societal resource to recipients who will most benefit. Although more than 17,000 patients are currently listed for liver transplantation, only about 7000 transplantations will be performed in 2008. Thus, any discussion of the indications for liver transplantation must address both the large number of patients for whom a liver transplant is appropriate as well as the factors that determine the far smaller number who ultimately undergo transplantation. This review will first focus on the general indications, evaluation, and process

for listing for transplantation without regard to the etiology of liver failure. However, it is important to recognize that the etiology of liver failure may influence the interpretation of the manifestations of liver failure, the timing of transplant evaluation, management of the patient while awaiting a transplant, and the potential benefit of transplantation on patient outcomes. For these reasons, we have organized the subsequent discussion according to the cause of liver disease.

### Referral for Transplant Evaluation

Referral for liver transplant evaluation should be considered for irreversible hepatic failure regardless of cause, complications of decompensated cirrhosis, systemic complications of liver disease, liver cancers, or liver-based metabolic conditions causing systemic disease (Table 1). Of course, the initial step in the evaluation process is this recognition of the need for a transplant and referral to a transplant center by the physician, usually a gastroenterologist. Certainly, many factors other than the presence of liver disease and liver failure enter into the decision of whether a patient is an appropriate candidate for transplantation. However, many of the contraindications to transplantation are relative or correctable, so these should probably not prevent referral of patients, particularly without discussion with the transplant center.

The timing of referral for a transplant has evolved in recent years, reflecting changes in the method of donor organ allocation. Waiting time was an important determinant of the patient's position on the transplant list until 2002. Thus, early referral and listing worked to the patient's advantage. In February 2002, the Model of End-

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*Abbreviations used in this paper:* INR, international normalized ratio; MELD, Model of End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease; PSC, primary sclerosing cholangitis; SVR, sustained virologic response; UNOS, United Network for Organ Sharing.

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**Table 1.** General Indications for Liver Transplantation

Fulminant hepatic failure
Complications of cirrhosis
Ascites
Encephalopathy
Synthetic dysfunction
Liver cancer
Refractory variceal hemorrhage
Chronic gastrointestinal blood loss due to portal hypertensive gastropathy
Systemic complications of chronic liver disease
Hepatopulmonary syndrome
Portopulmonary hypertension
Liver-based metabolic conditions causing systemic disease <sup>a</sup>
Primary oxaluria
Familial amyloidosis
$\alpha_1$ -antitrypsin deficiency
Wilson's disease
Urea cycle enzyme deficiencies
Glycogen storage disease
Tyrosemia

<sup>a</sup>May also cause liver disease.

Stage Liver Disease (MELD) score was implemented for determining donor liver allocation. The MELD score is a mathematical score determined from the patient's laboratory tests and is highly predictive of short-term mortality.<sup>1,2</sup> Thus, the MELD system offers an objective measure that is relatively free of bias and directs donor organs to those in greatest need irrespective of waiting time.<sup>1</sup> While patients can be listed for transplantation at any MELD score (there are no minimal listing criteria), there is no longer an advantage to early listing of patients with well-compensated cirrhosis.

**Pretransplant Evaluation**

The basic process of evaluation of transplant candidacy is relatively uniform between centers. Liver transplant evaluation generally follows the steps listed in Table 2. This process is necessarily rigorous and strives to answer 3 basic questions. First, are there other options short of transplantation that would serve the patient better or, stated another way, will liver transplantation offer the patient the best chance for long-term survival? Second, are there comorbid medical or psychosocial conditions that outweigh the benefit of transplantation or would preclude successful recovery from the procedure? Sometimes such contraindications are relative and can be resolved sufficiently to allow transplantation to proceed. Finally, what is the urgency of proceeding with transplantation? This is primarily determined by the MELD score, but there are exceptions that are discussed in the following text.

The standardized approach to the liver transplant evaluation detailed in Table 2 is designed to be completed within a few days, but this is often not possible. Many patients are quite ill and have other medical issues that require more extensive evaluation. For example, patients

with a history of smoking must undergo smoking cessation and pulmonary function testing. Patients with a history of substance abuse may require participation in a relapse prevention program. Patients with prior malignancy require an expert assessment of the risk of tumor recurrence. More commonly, patients are discovered to have a malignancy, usually hepatocellular carcinoma (HCC), or cardiac disease that requires more rigorous evaluation and treatment. Obesity may require dietary modification and weight loss. Management of diabetes

**Table 2.** The Process of Liver Transplant Evaluation

Event	Description
Referral	To transplant center or hepatologist
Financial screening	Secure approval for evaluation
Medical evaluation	
Hepatology assessment	Confirm diagnosis and optimize management
Laboratory testing	Assess hepatic synthetic function, electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumor markers, ABO-Rh blood typing; inulin clearance or 24-hour urine for creatinine clearance; urinalysis and urine drug screen
Cardiac evaluation	Electrocardiography and 2-dimensional echocardiography, stress testing and cardiology consult if risk factors are present and/or age 40 years or older
Hepatic imaging	Ultrasonography with Doppler to document portal vein patency, triple-phase computed tomography or gadolinium magnetic resonance imaging for tumor screening
General health assessment	Chest x-ray, prostate-specific antigen level (males), Pap smear and mammogram (females), colonoscopy if age 50 years or older or PSC
Transplant surgery evaluation	Assess technical issues and discuss risks of procedure
Anesthesia evaluation	Required if unusually high operative risk, eg, portopulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications
Ancillary support services	
Psychiatry or psychology	If prior history of substance abuse, psychiatric illness, or adjustment difficulties
Social work	Address potential psychosocial issues and possible impact of transplantation on patient's personal and social system
Financial counseling	Itemize costs of transplant and posttransplant care, help develop financial management plans
Nutritional support	Assess nutritional status and patient education

**Table 3.** Contraindications to Liver Transplantation

Absolute	
Active extrahepatic malignancy	
Hepatic malignancy with macrovascular or diffuse tumor invasion	
Active and uncontrolled infection outside of the hepatobiliary system	
Active substance or alcohol abuse	
Severe cardiopulmonary or other comorbid conditions	
Psychosocial factors that would likely preclude recovery after transplantation	
Technical and/or anatomical barriers	
Brain death	
Relative <sup>a</sup>	
Age	
Cholangiocarcinoma	
Portal vein thrombosis	
Chronic or refractory infections	
Human immunodeficiency virus infection	
Previous malignancy	
Active psychiatric illness	
Poor social support	

<sup>a</sup>See text for clarification.

and hyperlipidemia is best optimized before transplantation because these problems may worsen when the patient receives immunosuppressive agents. Of course, the timing of these evaluations and interventions is also influenced by the severity of the patient's illness and center-specific protocols.

### Contraindications to Transplantation

Contraindications vary between centers and over time. For example, the initial poor experience with transplantation of patients with hepatitis B led most centers in the United States to abandon transplantation for this indication for several years until hepatitis B immunoglobulin and then antiviral agents became available. Currently, these patients have excellent survival. Similarly, infection with human immunodeficiency virus was an absolute contraindication to transplantation in the past, but the availability of effective antivirals has led many centers to now consider these patients as potential candidates.

#### *Absolute Contraindications*

Some absolute contraindications remain and are unlikely to change. These are listed in Table 3 and include active extrahepatic malignancy or hepatic malignancy with macrovascular or diffuse tumor invasion, active and uncontrolled infection outside of the hepatobiliary system, active substance abuse, severe cardiopulmonary or other comorbid conditions that would compromise survival during and after transplantation, psychosocial factors such as the absence of social support or noncompliance that would likely preclude recovery after transplantation, and technical and/or anatomical barriers such as thrombosis of the entire portal and superior mesenteric venous system.

#### *Relative Contraindications*

Most contraindications to liver transplantation are relative. Age restrictions vary by site, but physiologic rather than chronologic age is most important. Elderly patients with comorbid conditions tolerate transplantation poorly, so most centers, rightly or wrongly, would hold the older patient to a higher standard of general health than they would a younger patient. Psychosocial contraindications such as psychiatric illness or poor social support can sometimes be resolved with time and intervention. Portal vein thrombosis is a relative contraindication, and the ability to perform the procedure hinges on access to a sufficiently large mesenteric vessel or collateral for anastomosis to the donor vein. Chronic or refractory infections such as osteomyelitis, pulmonary fungal infections, or atypical mycobacteria are addressed on an individual basis, but candidacy often depends on the availability and effectiveness of therapy. A history of a previous malignancy must be carefully considered when evaluating patients for transplantation. Generally, review of operative findings, pathology, and other therapies should be evaluated by an oncologist and an estimate of the likelihood of recurrence made. Each program must decide its tolerance for the risk of recurrent malignancy, but a risk of less than 10% within 5 years is a common standard.

### Listing for Transplantation and the Organ Allocation System

The results of the liver transplant evaluation are reviewed in detail by a patient selection committee composed of transplant surgeons, hepatologists, anesthesiologists, psychiatrists or psychologists, transplant coordinators, social workers, and a finance office representative. An oncologist, a cardiologist, or others who might offer insight on a particular case are often included on an ad hoc basis. The purpose of the committee is to determine whether the procedure is medically necessary and appropriate. Although a decision regarding the medical appropriateness and technical feasibility of transplantation is relatively straightforward, the ultimate decision to approve a patient for listing is much more difficult because it usually involves weighing other intangible factors. Patients must be sick enough to benefit but not too sick to make the procedure futile. They must not have comorbid conditions that would preclude recovery and restoration of health after transplantation. They must be able to behave as a reasonable long-term guardian of a limited societal resource. Thus, the committee decision weighs the potential for both individual and societal benefit from the procedure.

Approval by the committee leads to listing of the patient on the donor organ waiting list. Priority for organ allocation is highest for patients with fulminant hepatic failure who are listed as status 1 (Table 4). Since February 2002, all other patients have been listed in descending

**Table 4.** Recipient Listing Status

Status 1A
18 years of age or older
<u>and</u>
Fulminant liver failure (onset of encephalopathy within 8 weeks of first signs of liver disease <u>and</u> intensive care with ventilator dependence, requirement for dialysis or continuous venovenous hemodialysis, an INR >2.0, or acute decompensation due to Wilson's disease)
<u>or</u>
Primary nonfunction of a transplanted liver (aspartate aminotransferase level >3000 U/L and either INR >2.5 or acidosis within 7 days of graft implantation <u>or</u> anhepatic following removal of graft)
<u>or</u>
Hepatic artery thrombosis (aspartate aminotransferase level >3000 U/L and either INR >2.5 or acidosis within 7 days of graft implantation, <u>or</u> anhepatic following removal of graft; candidates with thrombosis within 14 days who do not meet the above criteria will be listed with a MELD score of 40)
Status 1B
Age less than 18 years
Chronic liver disease
Hospitalized in the intensive care unit with a calculated MELD or PELD score >25
<u>and</u>
One of the following:
Mechanical ventilation
Gastrointestinal bleeding requiring >30 mL/kg of red cell replacement in previous 24 hours
Renal insufficiency requiring dialysis or continuous venovenous hemodialysis
Glasgow Coma Score <10 within 48 hours of the listing
MELD
$0.957 \times \text{Log}_e(\text{Creatinine [mg/dL]}) + 0.378 \times \text{Log}_e(\text{Total Bilirubin [mg/mL]}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$
PELD
$0.436(\text{Age Younger Than 1 Year} = 1, \text{Older} = 0) - 0.687 \times \text{Log}_e(\text{Albumin [g/dL]}) + 0.480 \times \text{Log}_e(\text{Total Bilirubin [mg/mL]}) + 1.857 \times \text{Log}_e(\text{INR}) + 0.667(\text{Growth Failure} = 1)$

Growth failure is defined as less than 2 SDs below the norm for age and sex according to the current Centers for Disease Control and Prevention growth charts.

order according to MELD score (or Pediatric End-Stage Liver Disease [PELD] score for candidates younger than 12 years), with the highest scores receiving the highest priority for organ allocation. The MELD score is a mathematical score based on objective measures (serum creatinine and bilirubin levels and international normalized ratio [INR]) that quantify liver disease severity and is an accurate predictor of short-term mortality (Table 4).<sup>1,2</sup> The PELD score utilizes serum albumin and bilirubin levels and INR but also includes components for growth retardation and age younger than 1 year to account for short-term survival disparities in such patients (Table 4).<sup>3</sup> Calculated MELD scores range from 6 to 40. Listing status and MELD scores are regularly reassessed by the listing transplant center at intervals determined by disease severity. Patients who are status 1 or have a MELD score >25 must recertify every 7 days. Patients with

MELD scores of 19–24 must recertify monthly, and patients with MELD scores of 11–18 must be retested every 3 months.

The MELD score has been validated to predict 3-month and 1-year mortality in most patients with chronic liver disease.<sup>1</sup> The change to the MELD system for organ allocation has been extremely successful and has resulted in an increase in the average MELD score at the time of transplantation (calculated retrospectively for patients who underwent transplantation before implementation of the program), a reduction in median waiting time, and a reduction in wait list mortality while maintaining patient and graft survival.<sup>4</sup>

However, because the MELD score is based on short-term mortality risk, it might not be appropriate for some patients who are not at imminent risk of death but nonetheless derive benefit from transplantation. Perhaps the best example is the patient with compensated cirrhosis and HCC. Although the risk of death within 6 months might be quite low, the chance that the tumor might progress and therefore preclude lifesaving options such as transplantation is reasonably high. Thus, patients with stage T2 HCC are provided an exception score that offers them a reasonably high chance of receiving an organ offer before their tumor progresses to a point that would require them to be removed from the transplant list. The HCC exception score has been revised downward several times to accomplish this goal without offering these patients an unfair advantage over other patients at risk for dying or being delisted for other reasons.

Of course, HCC is not the only condition that might not be best served by the MELD system. Regional review boards composed of transplant physicians and surgeons from programs in each of the United Network for Organ Sharing (UNOS) geographic regions around the country were established in part to review such cases. They have struggled with these exception diagnoses and how to respond to requests for additional points without compromising waiting times or survival of those listed by their calculated MELD score. Some regions, including ours in Texas and Oklahoma, have established their own standardized criteria for exception scores; however, there is considerable regional variation in approval of exceptions.<sup>5</sup> In response to this dilemma, UNOS convened a consensus conference in 2006 to consider whether there were data to support exception scores for diagnoses other than HCC. The conclusions of that conference are listed in Table 5.<sup>6</sup> It is clear that more objective data are required before there can be further movement to standardize and expand exception scores.

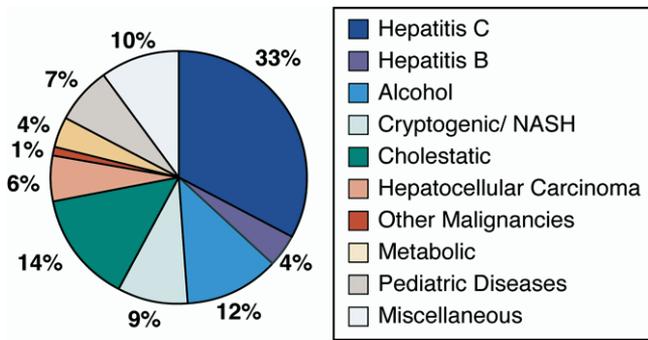
The process of organ allocation is mandated by UNOS regulations. Organs are allocated to local status 1 candidates first and then regional status 1 cases. If no status 1 candidate is listed in the geographic region, then organs are offered to the patient with the highest MELD score locally and then regionally.<sup>7,8</sup> Patients with a MELD score

**Table 5.** Summary of Conclusions of the MELD Exceptional Cases Study Group Conference Regarding Conditions That Might Not Be Adequately Addressed by the MELD Score<sup>6</sup>

Diagnosis	End point	Data required	Comments	Conclusion and recommendations
Manifestations of cirrhosis				
Ascites	Mortality	Serum sodium level	Subjective measure	Inadequate evidence to justify
Gastrointestinal bleeding	Mortality	Amount transfusion, contraindication to transjugular intrahepatic portosystemic shunt	Other therapy available	Inadequate evidence to justify
Encephalopathy	Mortality	Intracranial pressure monitoring, intubation/ventilation	Subjective measure and compliance issues	Inadequate evidence to justify
Hyponatremia	Mortality	Serum sodium level	Able to be manipulated, increased risk of central pontine myelinolysis	Inadequate evidence to justify
Hepatopulmonary syndrome	Hypoxemia	PaO <sub>2</sub> level ≤60 mm Hg while sitting, documentation of shunt	Correlation to wait list mortality not established	Yes, but need data regarding risk
Portopulmonary hypertension	Mean pulmonary artery pressure, pulmonary vascular resistance	Right ventricle function, response to vasodilators	Correlation to wait list mortality not established	Inadequate evidence to justify
Pruritus	None	None	Quality of life insufficient to justify priority	Inadequate evidence to justify
Miscellaneous liver diseases				
Budd–Chiari syndrome	Mortality	None	Acute Budd–Chiari syndrome listed as status 1A; others should use MELD points	Inadequate evidence to justify
Familial amyloidosis	Mortality, progression	Cardiac parameters, disability score, genotyping	Need information regarding wait list progression	Yes, because of risk of progression but data lacking
Cystic fibrosis	Mortality	Forced expiratory volume in 1 second <40%	Risk not well documented	Yes, if progressive pulmonary disease present
Hereditary hemorrhagic telangiectasia	Mortality	Cardiac failure, portal hypertension	Hepatic function maintained	Inadequate evidence to justify
Polycystic liver disease	Malnutrition	Nutritional parameters	Quality of life insufficient to justify priority	Inadequate evidence to justify
Primary oxaluria	Mortality	Renal function, liver biopsy	Risk of kidney loss justifies priority	Yes
Recurrent cholangitis	Mortality	Past septic complications	Need information that predicts mortality	Inadequate evidence to justify
Unusual metabolic disease	Mortality	Complications specific to disorder	Rare, so need to be addressed as individual petitions to regional review board	Inadequate evidence to justify
Malignancy				
Cholangiocarcinoma	Mortality	Metastatic survey, treatment history	Data inconclusive, studies under way	Inadequate evidence to justify
Unusual tumors	None	Pathology, metastatic evaluation	Rare, so need to be addressed as individual petitions to regional review board	Inadequate evidence to justify
Other				
Small-for-size syndrome	Mortality	Liver graft biopsy	Needs validation to quantitate	Yes

of 15 or less typically do not receive offers for organs because their short-term survival without a transplant on average exceeds that with a transplant.<sup>9</sup> The average MELD score of patients receiving offers for organs is

typically in the mid to high 20s, but this varies by geographic region, performance of local organ procurement, and the number of patients who are listed with MELD exception scores.



**Figure 1.** Proportion of liver transplants for specific etiologies, 1992–2007.

### Management While Waiting for Transplantation

All patients on the transplant list should be managed with the assistance of a transplant hepatologist. The aims are obviously to avoid unnecessary complications of cirrhosis, optimize management of complications when they occur, screen for changes in the medical condition such as worsening hepatic function or HCC that might change the priority for transplantation, and, above all, make sure that the patient is in the best possible condition when a donor organ becomes available. Thus, patients with higher MELD scores require more frequent observation than those with low scores.

Occasionally patients develop problems that may require that they be made temporarily inactive while remaining on the list (termed status 7) or permanently delisted. These problems might include development of extrahepatic malignancy or other comorbid conditions, change in social or financial situation, or, obviously, death.

When an organ becomes available, patients are admitted to the hospital for a brief evaluation to ensure that they are still appropriate candidates. At our center, the most common reasons for canceling transplantation are problems with the donor organ, interim medical problems, profound hyponatremia, development of pulmonary hypertension, or a positive drug or alcohol screen.

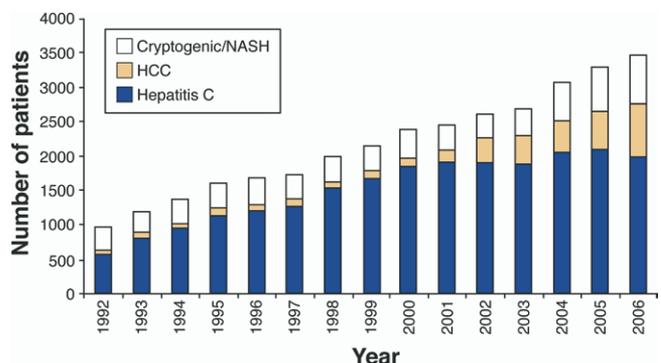
### Disease-Specific Considerations for Liver Transplantation

#### Hepatitis C

Hepatitis C virus (HCV) infects about 1.8% or 3–5 million persons in the United States.<sup>10,11</sup> Up to 20% of HCV-infected patients progress to cirrhosis after 20 years of infection.<sup>12</sup> Among patients with HCV-induced cirrhosis, 4% per year decompensate and 1%–4% per year develop HCC.<sup>13–15</sup> The risk of HCC is increasing among HCV-infected patients.<sup>16</sup> Five-year survival is only about 50% once hepatic failure has developed, so this is the clinical trigger point for referring patients for transplantation.<sup>14,15</sup> It has been projected that the number of

HCV-infected patients with hepatic decompensation or HCC will continue to increase over the next decade.<sup>11</sup> Indeed, complications resulting from chronic HCV infection account for 40% of liver transplants in the United States (Figures 1 and 2).

Antiviral treatment of chronic hepatitis C is effective in eradicating infection in approximately half of treated patients.<sup>16–18</sup> Viral clearance in patients with advanced fibrosis nearly eliminates the subsequent risk of liver failure and markedly reduces the chance of developing HCC.<sup>19</sup> While such an event has significant implications for the responding patient, it is unlikely that antiviral treatment will have a major impact on the overall future need for liver transplantation given the very small proportion of patients with chronic hepatitis C who are currently treated.<sup>11,12</sup> That being said, it is still imperative to attempt treatment before transplantation in patients who are able to tolerate therapy, because nearly all patients with chronic hepatitis C who undergo liver transplantation with detectable virus will reinfect the graft.<sup>20</sup> The optimal time to treat is before a patient develops advanced fibrosis or liver failure. Noncirrhotic patients have a 40%–80% sustained virologic response (SVR) to pegylated interferon and ribavirin, depending on their genotype.<sup>18,19</sup> In compensated patients with bridging fibrosis or cirrhosis, the SVR rate is about 10% lower than in patients without significant fibrosis, but SVR eliminates the risk of further progression and liver failure.<sup>20</sup> On the other hand, the risk of HCC remains, albeit at a significantly reduced rate.<sup>20</sup> Patients who have decompensated cirrhosis can still be treated with dose escalation and careful monitoring for dose-limiting cytopenia, but this should be done after they are evaluated and listed for transplantation. In this setting, SVR occurs in only 13% of patients with genotype 1 and 50% of patients with genotype 2 and 3.<sup>21</sup> Although these patients may still need a transplant, eradication of the virus (SVR) before transplantation eliminates the possibility of recurrence and therefore improves the long-term outcome post-transplantation.<sup>21</sup> Recent breakthroughs in HCV therapy with the advent of protease and polymerase in-



**Figure 2.** Number of transplants for cryptogenic cirrhosis, HCC, and chronic hepatitis C by year.

hibitors will likely allow us to achieve SVR in more patients, and this might conceivably lead to a decline in the need for transplantation in HCV-infected patients.

Patients with chronic hepatitis C who are evaluated for liver transplantation should clearly understand the risks of recurrent disease. Although the clinical course for patients with recurrent HCV after liver transplantation is variable, in general patients progress more quickly to cirrhosis. Rapid recurrence and graft loss due to fibrosing cholestatic hepatitis occur in 1%–10% of patients, and most of these individuals die within 1 year.<sup>22</sup> In those without fibrosing cholestatic hepatitis, 20%–40% develop cirrhosis in 5 years.<sup>23</sup> Decompensation occurs in 40% of cirrhotic patients within 1 year, and half of these patients die in the following year.<sup>23,24</sup> As a result, long-term survival of patients who undergo transplantation with HCV is inferior to that of patients who undergo transplantation for other indications.<sup>25</sup> Patients can be treated for HCV after liver transplantation, but SVR rates are low (10%–30%) because most have previously been treated unsuccessfully and cytopenias prevent achieving optimal doses in most cases.

### ***Hepatitis B and Other Viruses***

Chronic hepatitis B accounts for about 5% of liver transplants (Figure 1), but this number is decreasing due to better drugs to control the disease before liver failure occurs.<sup>26</sup> Liver transplantation was not always an option for patients with hepatitis B virus. The early experience was disappointing due to rapid recurrence of infection and graft loss.<sup>27</sup> Indeed, most centers stopped performing transplantation in such patients during most of the 1980s. Subsequently, the introduction of high-dose intravenous hepatitis B immunoglobulin reduced the chance of recurrence and allowed transplantation to be performed with excellent long-term survival.<sup>28</sup> Currently, the availability of nucleos(t)ide analogues has significantly reduced the need for liver transplantation and further improved outcomes in those who still require the procedure.<sup>26,29</sup>

Patients with active liver disease due to hepatitis B virus should be treated with antivirals.<sup>30</sup> Early recognition of infection and treatment of disease will prevent fibrosis progression and complications and reduce the need for eventual transplantation.<sup>31</sup> Nonetheless, some patients will still require transplantation because they are recognized late in the disease course, were inadequately treated, or develop HCC. It is still advisable to treat such patients while they await transplantation to reduce their viral load and risk of recurrence posttransplantation (antigenemia and liver disease). Nucleos(t)ide analogues decrease the viral load before transplantation and nearly eliminate the chance of chronic hepatitis B posttransplantation, particularly when used in combination with hepatitis B immunoglobulin.<sup>32</sup> While the optimal treatment regimen to prevent recurrence of hepatitis B virus

continues to evolve, most centers use hepatitis B immunoglobulin indefinitely with a nucleoside analogue.

### ***Alcohol***

Alcoholic liver disease alone accounts for 10%–12% of liver transplants in the United States, but it also contributes to more rapid progression of other causes of liver disease, particularly hepatitis C, to cirrhosis and hepatic failure.<sup>33</sup> All patients with alcoholic liver disease who are considered for liver transplantation must stop drinking all alcohol. Although there is no length of time of sobriety that guarantees abstinence following liver transplantation, most centers require a minimum of 6 months before patients can be listed for a liver transplant and many also require participation in a relapse prevention program. Justifications for a fixed period of abstinence pretransplantation include the lower rate of recidivism and the observation that liver function can improve significantly in some patients, sometimes leading to recovery to a point where transplantation is no longer required. During the evaluation for transplantation, a psychiatrist or psychologist should assess the patient's risk of recidivism and treat occult or apparent psychiatric illnesses. Risk scoring systems may also help predict recidivism posttransplantation.<sup>34</sup> Despite these precautions, patients who undergo transplantation for alcohol-induced cirrhosis have a 19%–33% risk of recidivism after liver transplantation.<sup>35,36</sup> Patients with insight into the role of alcohol in their liver disease and a prolonged period of abstinence are less likely to experience recidivism posttransplantation.<sup>35,36</sup>

Appropriately selected patients with alcohol-induced cirrhosis have excellent survival posttransplantation. In patients who experience a relapse, the pattern of drinking posttransplantation is variable, but even patients who return to occasional drinking rarely experience graft loss.<sup>36,37</sup> A minority of patients returns to abusive drinking, and this can result in graft loss and decreased survival.<sup>38</sup>

### ***Cryptogenic Cirrhosis and Nonalcoholic Steatohepatitis***

Cryptogenic cirrhosis currently accounts for about 9%–10% of liver transplants (Figure 1), and the proportion is increasing (Figure 2). Cryptogenic cirrhosis likely represents a diverse group of patients with liver disease resulting from a previous hepatic insult such as drug injury, alcohol use, resolved viral infection, autoimmune disease, or perhaps more commonly, nonalcoholic steatohepatitis.<sup>39,40</sup> Nonalcoholic fatty liver disease is unquestionably the predominant cause of cryptogenic cirrhosis. This is supported by the high prevalence of obesity, insulin resistance or diabetes, hyperlipidemia, and other manifestations of the metabolic syndrome among patients with this diagnosis.<sup>39,40</sup> Nonetheless, it is often difficult to attribute cryptogenic cirrhosis to nonalcoholic steatohepatitis with certainty because fat may de-

crease or completely disappear as cirrhosis ensues.<sup>41</sup> The reasons for this are not clear but might relate to weight loss due to hepatic decompensation, the catabolic state associated with cirrhosis, or metabolic changes in hepatocytes related to a decrease in portal blood flow. The risk of hepatic decompensation among patients with nonalcoholic steatohepatitis-induced cirrhosis is unknown and is likely similar to other nonviral causes of cirrhosis, although it has been estimated to be as high as 40%–60% within 5–7 years in some highly selected groups.<sup>41,42</sup> At any rate, these patients should be considered for transplantation early because many require weight loss or other lifestyle changes before becoming appropriate candidates. The transplant evaluation must be particularly rigorous in these candidates because they have an increased risk of death from cardiovascular and cancer-related diseases.<sup>43</sup> Nonalcoholic steatohepatitis can recur after liver transplantation, but it is uncommon in our experience and graft loss is rare.<sup>43</sup>

### ***Cholestatic Liver Diseases***

Primary biliary cirrhosis, primary sclerosing cholangitis (PSC), and secondary biliary cirrhosis are the most common causes of chronic cholestatic liver disease in adults. Primary biliary cirrhosis accounts for about 5% of liver transplants, but this number has gradually declined in recent years.<sup>26,44</sup> The course of the disease is reasonably well predicted by a mathematical model using common laboratory tests, and this has become useful in determining when to evaluate cases for transplantation.<sup>45</sup> Liver transplantation should be considered when the predicted 2-year survival begins to decline, and this usually coincides with the onset of hyperbilirubinemia or other manifestations of hepatic decompensation. If diagnosed early, ursodeoxycholic acid delays progression of the disease.<sup>46</sup> However, ursodeoxycholic acid appears to be ineffective once fibrosis develops.

PSC accounts for about 5% of all transplants. Although some patients with PSC undergo transplantation for hepatic decompensation, it is more common for them to develop dominant strictures with jaundice or recurrent biliary sepsis. Many become dependent on endoscopic or percutaneous biliary drains. Because these patients may not accumulate many MELD points, some regional review boards grant exceptions and extra points when patients experience recurrent biliary sepsis or tube dependence. All patients with PSC should receive a choledochojejunostomy at the time of liver transplantation. The incidence of recurrent PSC posttransplantation is debated but may occur in 15%–20% of patients.<sup>47,48</sup> There is a strong association between PSC and inflammatory bowel disease.<sup>49</sup> All patients with PSC should undergo a colonoscopy with biopsies regardless of age or symptoms to determine if they have inflammatory bowel disease. Patients with PSC and inflammatory bowel dis-

ease are at increased risk for colon cancer compared with patients with inflammatory bowel disease alone.

Secondary biliary cirrhosis is most often caused by a previous surgical procedure. However, pathologic obstruction of the biliary system by stones, malignancy, cysts, or parasites must be considered. Unfortunately, timely biliary decompression often fails to prevent progression of liver injury in these patients, who then may come to liver transplantation.

### ***Malignancy***

The incidence of HCC is rising, and it is estimated that up to 11,500 new cases of HCC now occur annually in the United States.<sup>15</sup> In the United States, the majority of cases is attributable to HCV. Currently, 1 in 5 patients with HCV disease who reaches transplantation has HCC (Baylor Regional Transplant Institute, unpublished data, January 2008). The proportion of liver transplants performed for HCC is increasing (Figure 2), a phenomenon that was predicted by earlier modeling studies of HCV disease prevalence.<sup>11</sup> Liver transplantation is restricted to patients who have limited tumor burden as defined by the Milan criteria and no evidence of macrovascular invasion (portal vein thrombosis) or metastasis. MELD priority is given to patients with stage T2 HCC who meet the Milan criteria: a single tumor  $\leq 5$  cm or up to 3 tumors with none exceeding 3 cm.<sup>50</sup> As a result, these patients are now more likely to reach transplantation without tumor progression,<sup>51</sup> and recurrence is extremely low with a 5-year survival rate of 71%–75%.<sup>52</sup>

Many centers have proposed expanding tumor size limits, and there is compelling evidence that a modest extension of criteria might be reasonable.<sup>53,54</sup> Others have proposed downsizing tumors by radiofrequency ablation, chemoembolization, radiotherapy, or other means. This remains controversial because it is not known whether downsizing sufficiently changes the biology of the tumor and therefore the likelihood of recurrence.<sup>55</sup> Although frequently performed, trials have not been conducted that definitely show that ablation pretransplantation reduces recurrence posttransplantation.

Cholangiocarcinoma is an aggressive malignancy with a poor prognosis. Most cases are associated with PSC.<sup>56</sup> Results following transplantation for cholangiocarcinoma have been disappointing due to early recurrence in half of patients and 5-year survival of only 23%.<sup>57</sup> Recently, the Mayo Clinic found that highly selected patients with cholangiocarcinoma who are treated with an aggressive protocol of radiotherapy and chemotherapy pretransplantation can achieve excellent survival posttransplantation.<sup>58</sup>

### ***Fulminant Liver Failure***

Fulminant hepatic failure is uncommon, and only about 2000 people present with fulminant hepatic failure in the United States each year.<sup>59,60</sup> Acetaminophen hep-

atotoxicity is currently the most common cause in this country, where it accounts for about 39% of cases. Approximately 65% of patients survive acetaminophen overdose without transplantation when appropriate treatment is provided early.<sup>61</sup> Idiosyncratic reactions to other medications are less common but have a worse prognosis. Other causes of fulminant hepatic failure include acute hepatitis A or B, Wilson's disease, autoimmune hepatitis, herbal supplement toxicity, cardiogenic liver failure, Budd–Chiari syndrome, pregnancy-related complications, diffuse liver metastases, and unknown causes.<sup>62</sup>

Prompt recognition and referral to a major medical center are crucial for evaluation and rapid listing for transplantation. Overall survival after liver transplantation has improved over the years as a result of better critical care and standardized protocols for management. It is important to decide early on if the patient is likely to recover and, if not, if he or she is a potential candidate for transplantation. In the latter group, transplant evaluation should be initiated immediately. Although clinical expertise plays an important role in management, several scoring systems have also been developed to predict outcome, including King's College criteria, Clichy criteria, and the MELD score. King's College criteria utilize different parameters depending on the etiology of liver failure (acetaminophen vs nonacetaminophen).<sup>63</sup> The Clichy criteria utilize the grade of hepatic encephalopathy and serum factor V activity, with transplantation recommended for patients with grade 3 or 4 encephalopathy or factor V levels less than 20% of normal.<sup>64</sup> Recently, a MELD score of more than 35 was also found to be an excellent predictor of mortality in adults with non-acetaminophen-induced fulminant hepatic failure.<sup>65</sup> Other parameters that have been reported to predict outcome include rising  $\alpha$ -fetoprotein, blood lactate, and phosphorus levels, but these have not replaced current criteria.<sup>66–68</sup> In practice, both these standardized criteria and good clinical judgment are required to ultimately decide who warrants transplant evaluation.

Currently, fulminant hepatic failure accounts for less than 5% of liver transplants. The most difficult part of management is controlling brain edema, renal failure, and infection while awaiting a suitable organ. Many patients die during this period, and others enter transplantation with complications of liver failure that ultimately cause their demise. Another difficult part of transplantation in this population is not knowing for certain whether a patient might recover without transplantation. This is why collective clinical judgment and team management are so important in these patients. Overall survival after liver transplantation is 40%–90%, depending on the etiology.<sup>69</sup>

### **Metabolic Diseases**

Metabolic disorders that may present with chronic liver disease in adulthood and ultimately require transplan-

tation include genetic hemochromatosis,  $\alpha_1$ -antitrypsin deficiency, Wilson's disease, and other more unusual causes. Overall, metabolic diseases are responsible for less than 5% of liver transplants in adults.

Genetic or hereditary hemochromatosis accounts for less than 1% of liver transplants. The outcome after transplantation is relatively poor, with 1- and 5-year survival rates of 64% and 34%, respectively.<sup>70,71</sup> The most common cause of death is sepsis due to uncommon pathogens.<sup>72</sup> The second most common cause of mortality post-transplantation is a cardiac complication.<sup>73</sup> A recent publication suggested that survival in patients with genetic hemochromatosis is now improving and approaching survival for other indications.<sup>74</sup> This might be attributable to better disease recognition, selection of transplant candidates, and adequate phlebotomy before transplantation.

$\alpha_1$ -Antitrypsin causes disease in about 3 million patients worldwide.<sup>75</sup> Among those with the PiZZ phenotype, it is estimated that only about 10% develop severe liver disease with portal hypertension and cirrhosis.<sup>76</sup> Heterozygous states may also be a factor that predisposes to more rapid progression of other forms of liver disease.<sup>77</sup>  $\alpha_1$ -Antitrypsin deficiency accounts for only about 1.6% of adult liver transplants. One- and 5-year survival rates are near that observed for other indications.<sup>78</sup> The recipient assumes the  $\alpha_1$ -antitrypsin phenotype of the organ donor and produces normal  $\alpha_1$ -antitrypsin levels within weeks of transplantation.<sup>79</sup> Whether this phenotype recovery has any impact on pulmonary function is still not known.

Wilson's disease is transmitted as an autosomal recessive defect that is associated with abnormal copper transport mechanisms that result in intrahepatic copper accumulation leading to progressive liver injury.<sup>80</sup> Increased copper deposition also occurs in other organs, including the brain, causing an array of neuropsychiatric manifestations, and the cornea, resulting in Kayser–Fleischer rings. Hepatic manifestations of Wilson's disease include chronic hepatitis, cirrhosis, or fulminant hepatic failure.<sup>80</sup> The diagnosis is often difficult because the disease can have such a varied presentation and laboratory results can be misleading. The hallmarks of the diagnosis are low serum ceruloplasmin level, a copper level in urine greater than 100  $\mu\text{g}/24\text{ h}$ , the presence of Kayser–Fleischer rings detected by slit lamp examination, and an elevated hepatic copper level  $>250\ \mu\text{g}/\text{g}$  dry wt.<sup>81</sup> Prompt diagnosis allows for the initiation of chelation therapy that may prevent further tissue injury.<sup>82</sup> Liver transplantation offers a cure of the metabolic defect. Long-term survival after transplantation is excellent, although survival is lower in patients with neurologic manifestations of their disease.<sup>83</sup> Thus, liver transplantation in patients with isolated or advanced neurologic deficits remains controversial.<sup>84,85</sup>

Although uncommon, patients with primary oxaluria, familial amyloidosis, Crigler–Najar syndrome, and urea cy-

cle defects can benefit from liver transplantation. Many of these cases present during childhood, but not necessarily.

### *Pediatric Indications*

The major reasons for liver transplantation in children are biliary atresia, cholestatic liver disease, metabolic disorders, malignancies including hepatoblastoma, and fulminant hepatic failure. Biliary atresia is the most common indication for liver transplantation in children and accounts for 41% of cases, of which about 25% occur in infants younger than 12 months.<sup>86</sup> It is a remarkable example of the success of surgical innovation and transplantation. Previously, biliary atresia was nearly always fatal without early liver transplantation. Currently, however, most patients undergo a Kasai portoenterostomy, which often restores bile flow from the liver and may prevent or delay the need for liver transplantation for many years.<sup>87</sup> Survival after liver transplantation for patients with biliary atresia is greater than 80%.<sup>88</sup> Other cholestatic disorders, including Alagille syndrome and sclerosing cholangitis, are the second most common indications for transplantation in children.<sup>86</sup>

Transplantation for metabolic disorders is a rewarding endeavor because it provides an opportunity to offer a definitive cure of the metabolic defect. The most common metabolic indication is  $\alpha_1$ -antitrypsin deficiency.<sup>89</sup> Cholestasis during infancy is the most common presentation, although this typically resolves spontaneously by 6 months of age. A small number of infants develop bile duct paucity with prolonged jaundice and cirrhosis.<sup>90</sup> Less common metabolic indications include urea cycle enzyme deficiencies, glycogen storage disease, Wilson's disease, tyrosemia, and primary hyperoxaluria.

Children with cystic fibrosis develop thick biliary secretions that plug the bile ducts, causing biliary obstruction, stasis choledocholithiasis, and occasionally sclerosing cholangitis. Secondary biliary cirrhosis leads to chronic cholestasis, loss of liver function, and portal hypertension. Infants with cystic fibrosis undergoing liver transplantation are a challenge because they often have advanced nutritional deficiencies due to exocrine pancreatic deficiency and/or short-bowel syndrome. Some have abnormal pulmonary function tests and are often colonized with *Aspergillus*.<sup>91</sup>

Children also develop primary hepatic malignancies in which liver transplantation offers the best treatment option. Hepatoblastoma treated with surgical resection and adjuvant chemotherapy before and after transplantation is now the standard protocol. This mode of therapy has achieved the best long-term survival rates.<sup>92</sup> HCC is less common in children.

Liver transplantation in children has evolved over the past decade to address the disadvantage they face with a limited donor pool of appropriate size. The PELD provides an advantage over adults for regional organ matching. Children can receive either a size-matched organ

from a deceased or living donor or an organ from an adult that has been reduced in size or split. This change has improved organ allocation in children but has not affected transplant outcomes.

### *Retransplantation*

Survival following liver transplantation has improved dramatically over the years due to better pretransplant care, improved anesthesia and surgical techniques, enhanced intensive care medicine, and more effective immunosuppressant medications. Early graft loss due to primary nonfunction of the graft or hepatic artery thrombosis accounts for 70% of graft loss during the first year and is routinely managed by early retransplantation.<sup>93-95</sup> However, late graft loss due to disease recurrence or chronic rejection occurs in a subset of patients in whom the only option for survival is retransplantation.

Primary liver diseases at risk for recurrence include hepatitis B and C, autoimmune hepatitis, primary biliary cirrhosis, and PSC. Recurrent hepatitis C is the most common. Late retransplantation is controversial, particularly for patients with recurrent hepatitis C.<sup>96</sup> Survival following retransplantation is inferior to that for primary grafts, with 3-year survival of only 40%–50%.<sup>93,95-97</sup>

### **Summary**

Patients should be considered for liver transplantation if they have evidence of fulminant hepatic failure, a life-threatening systemic complication of liver disease or a liver-based metabolic defect, or, more commonly, cirrhosis with complications such as hepatic encephalopathy, ascites, HCC, hepatorenal syndrome, or bleeding caused by portal hypertension. While the complications of cirrhosis can often be managed relatively effectively, they indicate a change in the natural history of the disease that should lead to consideration of liver transplantation. The decision regarding the appropriateness of transplantation should usually be left to the transplant center because the contraindications for the procedure are mostly relative, often manageable, and change over time. Evaluation includes a detailed medical evaluation to make sure that transplantation is technically feasible, medically appropriate, and in the best interest of both the patient and society.

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