Assessment for Liver Transplantation

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Selection of recipients for liver transplantation is based on 1) the severity and prognosis of the patient's liver disease; 2) related medical, surgical, and psychological factors; and 3) the desires of the patient. Severity of liver failure in patients with chronic liver disease is assessed by the Child-Pugh classification and the MELD (model for end-stage disease based) score. The Child-Pugh classification is based on empiric evaluation of 1) ascites, 2) encephalopathy, 3) prothrombin time, 4) serum bilirubin, and 5) serum albumin. The MELD score is based on 1) INR, 2) serum bilirubin, and 3) serum creatinine. The timing of placement of patients on the waiting list is based on assessment of stable versus decompensated cirrhosis. In the United States, patients are centrally listed and organs are first allocated to the sickest patient. Priority is given to patients with fulminant hepatic failure or primary allograft nonfunction. Suitability for transplant includes cardiac, pulmonary, renal, endocrine, oncological, infectious, nutritional, and psychological assessments.

Keywords: liver transplantation; Child-Turcotte-Pugh classification; porto-pulmonary hypertension; fulminant hepatic failure

Selection for Liver Transplantation

Evaluation of candidates for liver transplantation can be reduced to three core questions:

- What is the severity and prognosis of the patient's liver disease?
- Are there confounding medical, surgical, or psychological factors that would reduce the expectation of a successful liver transplant?
- What are the wishes of the patient in regard to liver transplantation?

These questions are best addressed in a multidisciplinary process. The evaluation may be carried out in an outpatient setting. The prospective candidate is assessed by transplant surgeons and physicians, social workers, and selected subspecialists including psychiatrists, cardiologists, pulmonologists, and nephrologists. Previous investigations including radiographs and biopsies are retrieved, and new investigations are ordered where necessary. When the information gathering segment of the evaluation is complete, the patient is presented to the transplantation evaluation committee and a decision is made regarding placement on the transplant waiting list.

Liver transplant programs must inform and educate prospective recipients and their families of the risks and benefits of liver transplantation. It is important to provide the patient with the opportunity to withdraw from transplant assessment if he or she does not wish to proceed. Conversely, whenever the transplant program determines that the patient is not a suitable candidate, the program should facilitate the patient in receiving a second opinion regarding their suitability, if they should so wish.

Assessment of Severity and Prognosis of Chronic Liver Disease

The severity of liver failure in patients with chronic liver disease can be assessed by several models, although the two models currently used are the Child-Pugh classification and the MELD score (model for end-stage disease).

Child-Turcotte-Pugh Class

This scoring scheme is an empiric compilation of four features of end-stage liver failure (Table 1):

- Ascites
- Encephalopathy

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Table 1 | **CHILD-TURCOTTE-PUGH CLASSIFICATION**

	POINTS		
VARIABLE	1	2	3
Encephalopathy	None	Moderate	Severe
Ascites	None	Slight	Moderate
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (sec. prolonged)	< 4	4-6	> 6
(INR)	< 1.7	1.7-2.3	> 2.3
Primary Biliary Cirrhosis/Primary Sclerosing Cholangitis			
Bilirubin	1-4	4-10	> 10

Scores are summed to determine Child's class: A = 5-6, B = 7-9, and C = 10-15.

CHILD-TURCOTTE-PUGH CLASSIFICATION

Based on (1) ascites, (2) encephalopathy, (3) prothrombin time, (4) serum bilirubin, and (5) serum albumin

- Prothrombin time
- Serum albumin

It was developed originally as an instrument to predict outcome after portacaval shunt surgery. Later Pugh modified it for a study of esophageal transection for bleeding esophageal varices and modified the score for patients with cholestatic diseases. It has been adopted as the most easily administered clinical tool to assess severity of cirrhosis. Survival of cirrhotic patients declines with worsening Child's class. The Child's class is useful for segregation of cirrhotic patients according to risk of dying. It does not indicate prognosis for an individual patient with cirrhosis. Furthermore, its origin as an empiric instrument for specific circumstances related to portal hypertension makes it less useful as a prognostic guide in many circumstances in which liver transplantation is under consideration. These include patients with chronic cholestatic diseases, liver tumors, or fulminant liver failure. The Child-Pugh classification has not been verified in childhood disorders.

MELD SCORE

Model for end-stage disease based on INR, serum bilirubin, and serum creatinine

MELD Score

The MELD score is based on the following three variables:

- INR (International Normalized Ratio)
- Serum bilirubin
- Serum creatinine

INR

International normalized ratio

To obtain the MELD score for any patient, access the Internet at www.unos.org or www.mayo.edu/int-med/gi/model/mayomodl-5-unos.htm

There are other prognostic scoring schemes:

- Primary biliary cirrhosis: sustained elevation of total bilirubin is the single most influential factor in predicting outcome. Patient age, serum albumin, prothrombin time, and the presence of edema are minor influential factors. The presence of cirrhosis is a weak prognostic factor.
- Primary sclerosing cholangitis: patient age, serum bilirubin, albumin, and aspartate transaminase, and a history of variceal hemorrhage have been constructed into a prognostic instrument. Although the allocation priority scheme in the United States does not incorporate prognostic scoring schemes specific to either primary biliary cirrhosis or primary sclerosing cholangitis, these scoring schemes allow transplant physicians to recognize patients with poor prognosis.

Timing of Placement on the Waiting List

A useful approach to the often difficult questions regarding timing of placement of a patient with liver disease on the transplant waiting list is to consider compensated (or stable) and decompensated cirrhosis.

Stable cirrhosis is defined as cirrhosis in a patient who has never experienced any one of the four cardinal features of decompensation: variceal hemorrhage, accumulation of ascites, jaundice associated with cirrhosis, or encephalopathy.

Decompensated cirrhosis: cirrhosis and the onset of at least one of these clinical phenomena is de-

Table 2 | **Indications for Consideration of Liver Transplantation in Patients with Chronic Liver Disease**

Recurrent gastroesophageal variceal hemorrhage
Refractory ascites
Spontaneous bacterial peritonitis
Severe hepatic encephalopathy
Hepatorenal syndrome
Profound nonresponsive pruritus of cholestatic liver disease
Severe hepatic osteopathy
Hepatocellular carcinoma
Progressive rise in serum alpha-fetoprotein without mass
Refractory bacterial cholangitis
Severe coagulopathy due to liver failure
Severe sustained fatigue and weakness
Severe malnutrition
Hepatopulmonary syndrome

fined as decompensated cirrhosis. The onset of decompensation is associated with significantly impaired survival and indicates the need to evaluate for liver transplantation. Spontaneous bacterial peritonitis and/or hepatorenal failure are indicators of significantly worsened prognosis and should prompt transplantation evaluation.

Indications for evaluation of liver transplantation are shown in Table 2. Paradoxically, some of these indications may, when severe, become contraindications to transplantation.

Transplantation for Non-Life-Threatening Disease

Liver transplantation is also indicated for conditions that cause unacceptable loss of quality of life:

- Lethargy: is associated with chronic liver disease. However, it is important to exclude treatable causes such as depression, hypothyroidism, or unwanted effects of medication.
- Pruritus: all therapeutic options are tried before transplantation, when liver function is well maintained. Such therapies include cholestyramine, cholestipol, rifampin, naltrexone, ursodeoxycholic acid, phenytoin, and plasmapheresis.
- Hepatic osteodystrophy: when progressive may be an indication for transplantation.

FULMINANT HEPATIC FAILURE (FHF)

The onset of acute hepatic encephalopathy within 8 weeks of the onset of symptomatic hepatocellular disease in a previously healthy person

Allocation and Distribution of Donor Livers

Different countries have adopted different approaches to allocation of cadaveric donors of solid organs for transplantation:

US: In the United States, there is no federal limitation on the number of transplant centers. Patients are centrally listed and available organs allocated to the individual recipient. At present, allocation gives priority to the sickest patient. The greatest priority is given to patients with fulminant hepatic failure or primary allograft nonfunction, and for certain pediatric indications. For all other candidates, priority is determined by the MELD or PELD (the pediatric scoring system) score. An adjustment has been made for patients with hepatocellular cancer. For an up-to-date account of these variations on the MELD/PELD scheme, consult the UNOS Web site (www.unos.org).

UK: The number of centers designated for NHS (public funded) treatment is controlled by central government. The six transplant units have areas (according to their contracted activity), and any organ offered in their area can be used for a listed patient. Supra-urgent patients (those with fulminant hepatic failure) will have national priority. The individual unit determines which recipient should receive donor

Table 3 | **Absolute Contraindications**

Severe (uncontrolled) infection outside the hepatobiliary system
Metastatic cancer (except some neuroendocrine cancers)
Extrahepatic cancer (other than local skin cancer)
Cholangiocarcinoma
Advanced cardiopulmonary disease
AIDS
Severe pulmonary hypertension
Technical considerations (e.g., widespread intraabdominal venous thrombosis)

Table 4 | **Relative Contraindications**

Recent drug or alcohol abuse
Age > 70 years
HIV infection, without AIDS
Inability to be compliant with immunosuppression protocol and/or participate in routine posttransplant medical follow-up
Advanced chronic renal disease
Moderate pulmonary hypertension

organs offered to that area. The units have agreed indications and contraindications to ensure equity and justice. (See www.uktransplant.org.uk)

Europe: European countries have adopted a range of approaches to organ retrieval, allocation, and distribution. For more information, see www.eurotransplant.nl.

Contraindications to Liver Transplantation

Absolute and relative contraindications to liver transplantation are shown in Tables 3 and 4.

Live Liver Donation

The use of live donors for liver transplantation was developed in response to the inadequate donor organ supply. Live liver donation began with left lobe resection from adults for transplantation into babies and small children. More recently, adult-to-adult transplantation, in which the right lobe of a healthy adult is resected and transplanted into an adult with severe liver disease, has been adopted by many transplant programs in North America and Europe. Live liver donation places the healthy living donor at risk and mandates that a careful selection process be applied to the donor. The mortality for a donor of a hepatic right lobe is up to 2%. In brief, a consensus has emerged that donors for adult-to-adult transplant must be

- Healthy
- Of identical or compatible ABO type
- Able to give informed consent and understand the risks of being a living donor
- Have sufficient body mass to provide a donor graft with a graft recipient
- Graft to recipient weight ratio (GRWR) of at least 0.8, and preferably 1.0., while leaving at least 25% of the native liver remaining in the donor.

The selection of recipients to receive a donor partial hepatectomy is less well defined. At the time of writing, there is an emerging consensus that adult-to-adult live liver donation should be offered to patients who demonstrate increased urgency without requiring ICU-based life support. Very ill unstable patients (i.e., patients requiring ICU-based life support) need a full-size graft. The very stable patient who is not in danger of foreseeable death can wait safely and may get a cadaveric organ. The patients most appropriate for receiving a graft from adult-to-adult living liver donation are those who have re-

covered from an episode of decompensation, those who manifest a gradual decline, and patients with newly diagnosed small hepatocellular cancer.

Assessment of Medical, Surgical, and Psychological Suitability

All patients must undergo full history and examination. History of vaccination and need for further vaccination is covered in the following article, "Management on the Liver Transplant Waiting List" by James Neuberger.

Cardiac Assessment

A history of systemic hypertension, angina pectoris, myocardial infarction, or age greater than 45 years necessitates a cardiology evaluation. This includes

- Chest radiography (standard in all patients)
- Stress cardiography
- Echocardiography
- In selected cases, coronary angiography (selected patients)

However, the degree of abnormality that precludes transplantation has not been established or agreed. The echocardiogram provides evidence of cardiac function and an estimate of pulmonary artery pressure (see porto-pulmonary hypertension below).

It is often difficult to interpret ejection fraction (EF) data in patients with end-stage liver failure and ascites. These patients have low systemic vascular resistance, and this lack of "afterload" means that even a cardiomyopathic heart can have an apparently "low normal" EF. No absolute thresholds of EF have achieved consensus for acceptance as a suitable candidate for liver transplantation. Similarly, there is no consensus on how to interpret a prior history of coronary artery bypass grafting or myocardial infarction, but many of these patients may be excluded from liver transplantation.

A history of symptomatic peripheral vascular disease should lead to formal evaluation of peripheral arterial flow. Significant claudication supported by flow data will usually exclude the patient from transplantation.

PORTO-PULMONARY HYPERTENSION

Idiopathic pulmonary hypertension associated with portal hypertension

HEPATOPULMONARY SYNDROME

Abnormal intrapulmonary shunts that result in VQ mismatch and hypoxia

Pulmonary Assessment

Clinical Evaluation

A history of dyspnea on moderate exertion, chronic cough, or any degree of hemoptysis are unequivocal warning signals of pulmonary disease.

If the peripheral oxygen saturation is low, arterial blood gases should be measured both lying and standing, with and without oxygen. A low oxygen saturation, which declines when the patient assumes a standing position (orthodeoxyia), suggests hepato-pulmonary syndrome. This requires full pulmonary investigation such as "bubble echocardiography" to assess vascular shunting.

Patients with symptomatic chronic obstructive pulmonary disease (COPD) or other evidence of significant pulmonary disease need

- Formal spirometry and
- Measurement of diffusion capacity

There are no absolute thresholds that determine that a patient is unsuitable for surgery or postoperative recovery.

Patients should be strongly advised to stop smoking cigarettes and other tobacco products whether or not there is manifest lung damage. However, most programs do not exclude patients who are unable to stop tobacco use.

Porto-Pulmonary Hypertension

Idiopathic pulmonary hypertension associated with portal hypertension is called porto-pulmonary hypertension. It is defined by high mean pulmonary artery pressure (MPAP) (normal < 25 mmHg), high pulmonary vascular resistance (PVR) (normal <120 dynes centimeters^{-5}), and normal pulmonary capillary wedge pressure (PCWP). Evidence of pulmonary hypertension on echocardiography requires right heart catheterization. Mild to moderate (MPAP <35 mmHg) poses no risk for transplantation. Severe porto-pulmonary hypertension is associated with high intra- and postoperative mortality. The utility of liver transplantation with simultaneous continuous administration of prostacycline, or combined liver-lung transplantation in patients with porto-pulmonary hypertension, is unknown.

Hepatopulmonary Syndrome

Portal hypertension may also be associated with abnormal intrapulmonary shunts that result in VQ mismatch and hypoxia. This is called hepatopulmonary syndrome. Hepatopulmonary syndrome may gradually resolve after successful liver transplantation, although the restoration of arterial partial pressure of oxygen (PaO_2) to normal may take months.

Cystic Fibrosis

The colonization of the affected lungs by *Burkholderia cepacia* is an absolute contraindication.

Renal Assessment

Many patients with acute or chronic liver failure have concomitant impairment of renal function. The causes of renal failure in patients with serious liver disease include

- Established parenchymal kidney injury either related to the cause of liver disease (such as HCV infection) or independent of it
- The patient with end-stage liver failure is at risk for acute insults to the kidney as a consequence of the acute decompensation such as
  - A result of interventions and therapies which compromise the kidney as due to overuse of diuretics or nephrotoxic drugs and contrast medium
  - Hypotension
  - Hepatorenal failure. This is a complex disorder in which homeostatic mechanisms in the splanchnic and renal vasculature act together to produce a "pre-renal type" renal failure in which there is vasoconstriction of the intrarenal arterioles, and avid retention of sodium from the glomerular filtrate. Treatment is by correction of intravascular volume contraction (usually with albumin) and occasionally glypressin, somatostatin, midodrine, TIPS

The assessment of renal function:

- Inspection of urine
- Laboratory investigation of the urine for protein, blood, and electrolytes
- Measurement of serum creatinine

Microscopy

Microscopy of the urine may reveal nephritic sediment (red cell casts, white cell casts).

Low Urinary Sodium

Hepatorenal syndrome and prerenal uremia both produce avid retention of filtered sodium and reduced urinary sodium. Urinary sodium is measured on a "spot urine," and a level less than 10 mEq per ml is the standard threshold for recognizing sodium retention. This result is confounded by recent exposure to loop diuretics.

Urinary Protein

Many patients with end-stage liver failure have peripheral edema and reduced serum albumin concentrations. Hypoalbuminemia in cirrhotic patients is often attributed to synthetic failure, and it is easy to overlook renal protein loss. Diabetic renal disease or glomerulonephrititis associated with chronic infection with hepatitis B or C are common causes of nephrotic syndrome in "liver patients." Spot urine protein levels should be checked in all candidates for liver transplantation and a formal 24-hour collection made in anyone with detectable protein.

Glomerular Filtration

Serum creatinine is an inaccurate indicator of glomerular filtration in cirrhotic patients, especially those with ascites or malnutrition. Formal measurement of glomerular filtration rate is appropriate whenever there is concern that the full extent of renal impairment might be masked. An elevated serum creatinine has been repeatedly found to be an independent risk factor predicting a worse outcome after liver transplantation.

There are many causes for lowered graft and patient survival in patients with elevated serum creatinine prior to transplantation, suggesting that serum creatinine is acting as a surrogate for many high-risk factors.

SUBFULMINANT HEPATIC FAILURE

The onset of acute hepatic encephalopathy within 9-26 weeks of the onset of symptomatic hepatocellular disease in a previously healthy person

Combined Liver-Kidney Transplantation

There is controversy about the relative value of isolated orthotopic liver transplantation in the face of established renal failure, compared with combined liver kidney transplants. If the kidney failure is mainly due to hepatorenal syndrome, then the patient should receive an orthotopic liver transplant only. If there is advanced intrinsic kidney disease, serious consideration must be given to dual organ replacement.

Endocrine Assessment

Diabetes

Many patients with end-stage liver failure are diabetic or have insulin resistance. Retrospective analysis suggests that persons with diabetes mellitus requiring insulin or hypoglycemic tablets therapy have a worse outcome after transplantation, as a result of cardiac, renal, or microvascular damage. The value of pancreas transplantation in diabetic patients undergoing liver transplantation is controversial and probably should be confined to centers studying combined transplants according to a prospective protocol.

Sexual Endocrinology

Many women capable of menstruation experience amenorrhea as a result of end-stage liver failure. Specific investigation of "ovarian failure" is not necessary in these circumstances. Menstrual periods are restored in 80% of these women within 3 months of successful liver transplantation.

Male impotence is common in end-stage liver failure. While liver transplantation may restore male sexual function, the causes are often multifactorial (especially diabetes, and drugs such as antihypertensives).

Thyroid Disease

Thyroid disease (hypo- or hyperthyroidism) is associated with many chronic liver diseases, and thyroid function should be routinely checked in all and corrected where appropriate. In the sick patients, pseudo-hypothyroidism may be present but does not require intervention.

Assessment for Primary Hepatic Malignancy

Primary Liver Cell Cancers

Hepatocellular Carcinoma

The development of liver cell cancer is suggested by the development of space-occupying lesions on liver imaging or a rising serum alpha-fetoprotein level.

All candidates for liver transplantation should undergo a careful evaluation for cancer, including

- Measurement of serum alpha-fetoprotein
- Imaging of the liver parenchyma. The choice of cross-sectional image of the abdomen includes sonography plus Doppler studies, spiral CT, or MR imaging

Analysis of the UNOS database up to 1996 shows a 5-year survival for all patients undergoing liver transplantation for malignant neoplasms to be 35.4% (n = 796), compared with 72.3% for all liver transplants (n = 20,063). In contrast, acceptable outcomes occur when tumors meet the following criteria:

- Small unifocal hepatocellular carcinomas, defined as less than 5 cm in greatest diameter
- Few multifocal hepatocellular carcinomas, defined as up to three tumors whose greatest diameter is no more than 3 cm
- Without evidence of vascular invasion or extrahepatic spread

Biopsy confirmation of a tumor is usually contraindicated, as it is likely to spread the tumor along the biopsy track.

Other Primary Liver Cancers

"Slow growing" tumors such as hepatoblastomas and neuroendocrine tumors are occasionally considered appropriate for transplantation.

Cholangiocarcinoma

There is general agreement that patients with cholangiocarcinoma should not receive liver transplantation, except within a defined research protocol.

The detection of cholangiocarcinoma is often difficult.

Extrahepatic Malignancy Screening and Those with a Past History of Cancer

A past history of malignancy provides a difficult challenge for the transplant assessment team to determine how many disease-free years are required to reduce the chance of recurrence to an acceptable minimum.

All adult women need gynecologic assessment including "Pap" cervical cytology smear. Women over 40 years should undergo mammography.

All patients greater than 40 years should be considered for occult colon cancer with hemoccult testing followed by colonoscopy wherever the screening is positive. Where there is a higher risk, as those with ulcerative colitis, a colonoscopy should be done. Sigmoidoscopy is inadequate, as there is a high incidence of right-sided colon cancers.

All men older than 45 years should undergo testing for prostatic specific antigen (PSA).

Assessment for Infection

TB

Screening for tuberculosis includes chest radiograph and, in patients at risk, placement of PPD (purified protein derivative). Candidates who are PPD positive may be treated with antituberculosis monotherapy (e.g., Isoniazid for 6 months) prior to transplantation, or treatment may be postponed until after the transplant.

HIV

All patients should be screened for antibodies to human immunodeficiency virus (HIV). The role of liver transplantation in HIV-infected patients with end-stage liver failure is controversial.

Other Viruses

Antibodies to hepatitis A, B, and C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV) are measured as baseline studies.

In the case of CMV, the viral status of the donor and recipient predicts the risk of CMV disease after transplant.

Nutritional Assessment

Protein and Calories

Many patients with end-stage liver failure are malnourished, and malnutrition is associated with a poor outcome after transplantation. Unfortunately, it is difficult to restore nutritional well-being in outpatients with liver failure. Many liver patients are already on restricted diets: sodium restriction to diminish poorly controlled ascites, protein restriction to control recurrent hepatic encephalopathy, and fluid restriction in hyponatremic patients.

Most cirrhotic patients, even those with intermittent hepatic encephalopathy, can tolerate 80 grams of protein per day.

Vitamins

People with chronic cholestasis and those on bile acid sequestrants (such as cholestyramine) are at risk of malabsorption of fat-soluble vitamins.

- Vitamin K should be used in patients with prolonged clotting
- Vitamin D levels (serum 25 hydroxycholecalciferol) should be measured and replenished where needed
- Vitamin A replacement should be considered when there is the possibility of deficiency

Bone Disease

Patients with chronic liver disease may have many reasons for excessive bone loss: chronic cholestasis, corticosteroids, chronic alcoholism, and postmenopausal state in women.

Bone densitometry should be considered in

- Female candidates above the age of 45 years
- Patients who have received corticosteroids for at least 1 year
- Patients with a history of chronic cholestatic disorders

Treatment

- Supplementation with Vitamin D and calcium as appropriate
- Add etidronate or palmidronate in patients shown to be osteoporotic

Nutrition

Patients with cirrhosis from any cause tend to be malnourished. Malnutrition is associated with a poor outcome after liver transplantation. Reasons for malnutrition include

- Anorexia (common)
- Inappropriate dietary advice. In particular, patients with end-stage liver failure should be encouraged to ingest up to 2 grams/kg of protein per day. The risk of hepatic encephalopathy from dietary protein has been overstated.
- Malabsorption
- Associated pancreatitis
- Associated celiac sprue (associated with autoimmune hepatitis and PBC)

Where there is evidence of malnutrition, candidates for transplantation should have a formal assessment of their nutritional state. This should include

- Dietary assessment
- Height, weight, and body mass index (measured as weight(kg)/height(m2))

If there is evidence of malnutrition:

- Assessment of possible malabsorption
- Assessment of nutrition: measure mid-arm circumference and skin-fold thickness
- Give dietary advice: aim for calorie intake 35-50 kcal/kg ideal body weight and, unless hepatic encephalopathy is a clinically significant problem, ensure the daily protein intake is at least 1.3-1.5 g/kg ideal body weight
- If the patient cannot tolerate such an intake, consider nutritional supplements

Obese patients are at greater risk of morbidity and mortality after transplantation and therefore should be advised to lose weight.

Surgical Assessment

There are few surgical contraindications to liver transplantation. Any prior surgery in the right upper quadrant increases the risk of surgery and probable blood loss. Extensive thrombosis of the portal venous system including the superior mesenteric vein may preclude transplantation. Careful radiological assessment is mandatory in these patients. Angiography remains the gold standard, but in many instances, magnetic resonance (MR) scanning with gadolinium angiography has largely replaced formal angiography, avoiding intravenous contrast in patients with marginal renal function.

Psychological Assessment

All patients should be assessed for any psychological factors that might affect the survival and quality of life after transplantation. The transplant evaluating team must seek the opinion of psychiatric experts to assess prognosis of the psychiatric disorder. The psychological assessment may be confounded by hepatic encephalopathy. Patients with a combination of end-stage liver failure, hepatic encephalopathy, and a history of significant psychiatric disorder present some of the most difficult dilemmas that come before the transplant evaluating team.

Assessment for Patients with Alcoholic Liver Disease and a History of Drug Addiction

More than 80% of transplant programs in North America and Europe include assessment by a psychiatrist or addiction specialist in the evaluation of patients with alcoholic liver disease. Assessment is directed to determining the likelihood that the candidate will remain abstinent from addictive substances both before and after transplant and will comply with all aspects of follow-up.

Although it remains controversial as an indicator of future abstinence, the great majority of liver transplant programs in North America and Europe either require or place a value on a period of abstinence in determining whether to place an alcoholic patient on the waiting list. Many programs will use an approach that also assesses the patient's acceptance of alcoholism, their social support to remain abstinent, and their use of behavior modifying programs such as Alcoholics Anonymous. Whether such assessments distinguish accurately future drinkers from abstainers remains in doubt.

Many programs insist that the alcoholic or addicted candidate participate in addiction therapy as a prerequisite to either placement on the transplant list or reception of a donor liver. The degree of

Table 5 | **Clinical Grades of Acute Hepatic Encephalopathy**

Grade	Mental State	Asterixis Findings	Electroencephalogram
I.	Altered affect, subtle loss of mental acuity, slurred speech	Slight or none	Normal
II.	Accentuation of stage I, drowsiness, inappropriate behavior, loss of sphincter control	Easily elicited	Abnormal, generalized slowing
III.	Sleepy but rousable, marked confusion, can answer simple questions only	Present when patient can cooperate	Always abnormal
IV.	Coma	Cannot cooperate	Always abnormal
IVa.	Responds to pain		
IVb.	No response to pain		

physical impairment due to liver failure dictates the capacity of the candidate to acquiesce to required treatment. Furthermore, there is no consensus on how best to manage a patient found to have returned to alcohol use while waiting for transplantation. Many centers will "recycle" the patient through alcoholism assessment and reconsider replacement on the list after achieving a certain period of sobriety. This period is usually set arbitrarily at 6 months.

It remains uncertain whether the presence of a major psychotic disorder (bipolar disease, unipolar depression, and schizophrenia) should preclude liver transplantation. Candidates who carry a diagnosis of major psychosis are often functional on therapy.

Specific Disorders

Fulminant and Subfulminant Hepatic Failure (FHF, SHF)

Acute hepatic injury presents as a sudden increase in previously normal liver transaminase. Acute hepatic injury in the absence of hepatic encephalopathy almost always resolves.

FHF is defined as the development of acute hepatic encephalopathy (see Table 5) within 8 weeks of the onset of symptomatic hepatocellular disease in a previously healthy person.

Subacute hepatic failure is also termed submassive hepatic necrosis, subfulminant hepatic failure, subacute hepatic failure, and late-onset hepatic failure. It is defined by the development of acute hepatic encephalopathy within 9 to 26 weeks of the onset of symptomatic hepatocellular disease in a previously healthy person. It is characterized by a slow and fluctuating illness, with usually mild encephalopathy and progressive ascites. Unlike FHF, the INR is rarely more than 3.0. These patients usually die unless they are transplanted.

Cerebral edema, leading to increased intracranial pressure (ICP), is a common feature of severe fulminant hepatic failure and may cause permanent cerebral injury and death. The onset of cerebral edema may occur during surgery and in the first 48 hours posttransplantation. Fulminant hepatic failure and submassive hepatic necrosis are always accompanied by severe coagulopathy.

The causes of fulminant hepatic failure are shown in Table 6.

Acetaminophen toxicity is the most common cause of acute liver injury and fulminant hepatic failure in Great Britain. Alcoholics, those on enzyme-inducing drugs, and those who are malnourished are at particular risk of acetaminophen-induced hepatic failure. Acetaminophen-induced liver injury in alcoholics is the most common cause of fulminant hepatic failure in the United States.

Acute viral hepatitis is an important cause of both fulminant and subfulminant failure.

In many cases, the cause of FHF is not clear and there are no serological clues as to the diagnosis. These patients are often classified as non-A, non-B, non-C hepatitis, but a more accurate term is seronegative hepatitis as there is usually no evidence for a viral cause

The causes of subfulminant hepatic failure are similar to those for FHF, once the causes of the most acute forms of acute hepatic injury such as acetaminophen-induced liver injury have been omitted.

Ischemic hepatitis (also called "shock liver") usually recovers with medical support.

Most patients with FHF have a small, shrinking liver. An enlarged liver is associated with either venous-outflow obstruction or infiltration by tumor. In such cases, where venous-outflow obstruction has been excluded by imaging, a liver biopsy should be considered.

Table 6 | **Causes of Fulminant Hepatic Failure and Subfulminant Hepatic Failure**

Viral Infection
Hepatitis A
Hepatitis B
Hepatitis B and D
Hepatitis C
Other viruses (less common)
Herpes (in immunosuppressed persons, including pregnant women)
Cytomegalovirus
Epstein-Barr
Varicella
Adenovirus
Poisons, Chemicals, and Drugs
(Note: assume that ANY drug, herbal remedy, or toxin may be associated with liver damage)
Amanita phalloides
Acetaminophen (paracetamol)
Halogenated volatile anesthetics (especially halothane)
Isoniazid and other anti-TB medication
Valproate
Monoamine oxidase inhibitors
Ecstasy
Ischemia and Hypoxia
Hepatic vascular occlusion
Acute circulatory stroke
Heat stroke
Gram-negative sepsis
Miscellaneous
Acute fatty liver of pregnancy
Reyes syndrome
Wilson's disease*
Hodgkin's disease and other lymphomas
Malignant infiltration
Hereditary fructose intolerance
Galactosemia, tyrosinemia
Idiopathic hepatitis (also called non-A to non-E)

*Strictly not FHF as almost all patients have established cirrhosis at the time of presentation.

Predicting Outcome in Fulminant Hepatic Failure and Subacute Hepatic Necrosis

In general, the deeper the coma, the worse the outcome. Paradoxically, rapid onset of encephalopathy is a favorable prognostic sign, whereas delay in the onset of encephalopathy after the onset of jaundice indicates a lack of spontaneous recovery and is an unfavorable prognostic factor. Consequently, most acetaminophen-induced fulminant hepatic failure patients who experience grade III coma recover spontaneously, while submassive hepatic necrosis has a particularly poor outcome.

Criteria for determining the prognosis of fulminant hepatic failure are shown in Table 7.

These criteria separate acetaminophen-induced FHF from all other causes. Drug-induced hepatic failure, other than that caused by acetaminophen, has a poor prognosis. Examples include hepatic failure due to phenytoin or halothane. HBV- and HAV-induced hepatic failure have a better outcome than idiopathic (presumed viral) fulminant hepatic failure. Patients younger than 2 years or older than 40 years have a poor prognosis. Renal failure is also a poor prognostic factor. Some have recommended serum factor V levels as an indicator of when to proceed to transplant. A factor V level of less than 20% is a poor prognostic indicator. Acidosis is a valuable prognostic factor, par-

Table 7 | **Prognostic Criteria for Predicting Requirement of Liver Transplantation in Patients with Fulminant Hepatic Failure**

Acetaminophen Toxicity:
pH < 7.3 (irrespective of grade of encephalopathy)
or
Prothrombin time > 50 seconds and serum creatinine > 3.4 mg/dL (300 mmol/L) in
Patients with grade III or IV encephalopathy:
Arterial blood lactate > 3.5 mmol/l is associated with a high mortality
All Other Causes:
Prothrombin time > 50 seconds (irrespective of grade encephalopathy)
or
Any three of the following variables (irrespective of grade of encephalopathy):
Age < 10 years or > 40 years
Liver failure due to halothane or other drug idiosyncrasy or idiopathic hepatitis
Duration of jaundice prior to encephalopathy > 7 d
Prothrombin time > 25 seconds
Serum bilirubin > 17.5 mg/dL (300 mmol/L)

Adapted from O'Grady et al. **Gastroenterology 1989;97:439**. The prothrombin time thresholds have been reduced for application in the United States due to differences in laboratory methods to assay prothrombin time between Europe and US. In Europe, prothrombin times should be multiplied by 2.

ticularly in acetaminophen-induced fulminant hepatic failure.

While listed and awaiting a suitable donor organ, the patient may deteriorate (sepsis, cardiovascular or pulmonary failure, or cerebral edema), which may make transplantation impossible. For this reason, human heterotopic auxiliary transplants, live donor segmental liver transplantation, extracorporeal perfusion through human or pig livers or artificial hepatocyte perfusion devices, and xenografts have been attempted to sustain the patient until spontaneous recovery develops or a suitable organ is found.

Chronic Hepatitis C

The problem of chronic hepatitis C relates to the recurrence after transplantation. Strategies to reduce HCV RNA are currently being evaluated.

Hepatitis B Infection

HBV: Markers for active viral replication such as HBeAg and HBV DNA used to be considered relative contraindications to liver transplantation. The advent of antiviral agents including lamivudine and postoperative management protocols using HBIg has allowed successful transplantation in high-risk patients. Patients who have circulating HBV DNA should receive treatment with lamivudine while awaiting transplantation. Antibodies to hepatitis D should be measured in HBsAg-positive patients. Co-infection by hepatitis D ameliorates the severity of posttransplant hepatitis B infection.

Hemochromatosis

Patients with hemochromatosis have a worse outcome after liver transplantation than patients with other diagnoses. Some of this effect is due to failure to recognize hemochromatosis during the pretransplant evaluation. All candidates should have serum iron, transferrin and transferrin saturation, and ferritin estimated. We recommend the measurement of the hemochromatosis gene test (HFE) in anyone with iron saturation in excess of 45% or in anyone with a suggestive history for hemochromatosis (personal or family history of diabetes, cirrhosis, and arthritis). HFE is positive as a homozygous test for the major allele (C282Y) or heterozygous for both the major and minor allele (H62D) in 80% or more of affected persons, depending on the ethnic diversity of the population in question. Diabetic candidates for liver transplantation need particularly careful cardiac assessment.

Primary Sclerosing Cholangitis

Colitis and Colon Cancer

Those with PSC and inflammatory bowel disease (IBD) have a greater risk of both cholangiocarcinoma and colon cancer than patients with IBD alone. Since the colon cancer is likely to develop in the

right colon, all patients should have a colonoscopy to assess the presence and degree of colitis as well as exclude colon cancer. Colectomy at the time of transplantation does not seem to add to the risks of the procedure.

Cholangiocarcinoma

Because the tumor spreads early along the lymphatics and nerves, the detection of cholangiocarcinoma is a contraindication for transplantation. Exclusion of cholangiocarcinoma is difficult as the tumors are often not visualized on imaging, whether by ultrasound, CT, MR, or PET scanning. Bile cytology, while specific, is not sensitive, and ERCP is associated with a risk of inducing severe cholangitis and/or pancreatitis. Serum markers, such as CEA and CA19-9 may help but have not the specificity nor sensitivity required.

Non-Alcoholic Fatty Liver

Non-alcoholic steatohepatitis (NASH) and it's variant non-alcoholic fatty liver disorder (NAFLD) are terms used to describe an idiopathic clinicopathological spectrum of disorders characterized by macrovesicular and microvesicular deposition within hepatocytes. NASH is associated with histologic appearances of inflammation in the hepatic lobule often with Mallory's hyaline, in the absence of alcohol consumption. NASH occurs in conjunction with insulin resistance, obesity, and hyperlipidemia, although not all patients exhibit all of these elements of the syndrome. NASH may progress to fibrosis within the liver and is thought to be an important cause of cryptogenic cirrhosis. Some patients with cryptogenic cirrhosis thought to be due to NASH progress to liver failure are candidates for liver transplantation.

Celiac Sprue

Because of the association between celiac sprue and autoimmune disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis, all Caucasian candidates for orthotopic liver transplantation should be screened for celiac disease by measurement of serum antiendomysial antibodies. When positive, a duodenal biopsy is mandatory.

Retransplantation

Early Retransplantation

Early retransplantation (usually defined as within the first 30 days) is required for primary allograft nonfunction, hepatic artery thrombosis, and massive hemorrhagic necrosis. Such patients behave like those with fulminant hepatic failure and require emergency placement on the waiting list.

Late Retransplantation

Late retransplantation is required for management of graft failure due to recurrent disease, vascular or biliary problems, or chronic ductopenic rejection. Survival is less than that observed for primary graft recipients. Retransplantation on account of recurrent viral hepatitis has a poor outcome due to aggressive recurrence of the underlying disorder. Further attempts at rescue with second, third, or fourth grafts are associated with progressively poorer outcomes in mortality and morbidity.

Suggested Reading

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5. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. **N Engl J Med 2002;346:1074-82**.
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