

Liver Transplantation: Indications, Pretransplant Evaluation, Surgery, and Posttransplant Complications

Alan Koffron, MD, FACS*, Julie A. Stein, MD

*William Beaumont Hospital, 3601 West Thirteen Mile Road,
Royal Oak, MI 48073, USA*

Liver transplantation is the therapeutic option of choice for acute and chronic end-stage liver disease. The indications and contraindications to liver transplantation have become established, as has the operative and post-operative management. This article provides a practical clinical approach to the evaluation and management of patients with acute and chronic liver failure, with particular emphasis on liver transplant recipient selection, clinical management, and complications. The goal is to provide helpful guidelines to caregivers involved in the multidisciplinary care of these complex patients.

Liver failure can be either acute (fulminant or subfulminant failure) or chronic (decompensated cirrhosis). Each disease entity presents unique features with important differences between the two entities. In the pretransplantation era, liver failure was nearly universally fatal, with mortality from fulminant hepatic failure of 80% to 90%, and 1-year mortality in decompensated cirrhosis of more than 50%. In contrast, liver transplantation patient survival is presently more than 85% at 1 year and more than 70% at 5 years, emphasizing the clinical benefit of liver transplantation for either acute or chronic liver failure. Both split-liver and live-donor liver transplantation (LDLT) offer additional hope to patients with liver failure in the presence of an ever-growing cadaveric organ shortage.

Liver transplantation for acute liver failure

Acute liver failure (often used synonymously with fulminant liver failure) is defined as acute hepatic deterioration without antecedent chronic liver

* Corresponding author.

E-mail address: alan.koffron@beaumont.edu (A. Koffron).

disease, which has progressed from the onset of jaundice to the development of hepatic encephalopathy in less than 8 weeks [1]. The evaluation and management of acute liver failure is complex and clinically evolving. This article focuses on the management of acute liver failure regarding liver transplantation. Acute liver failure is reviewed in detail elsewhere in this issue.

Refinements in the definition of acute liver failure include a distinction between fulminant (<2 weeks) and subfulminant hepatic failure (>2 weeks), a difference that reflects the greater predominance of brain edema and intracranial hypertension in patients with the shorter interval. Both drug-induced hepatic failure and an indeterminate etiology seem to be more commonly associated with a longer interval. In a review of 295 cases in the United States, acetaminophen intoxication was the leading cause, followed by non-A-E (cryptogenic) hepatitis, and drug-induced liver failure (Table 1) [2]. Acetaminophen toxicity has the best spontaneous survival (60%). It is important to recognize that acute ingestion of merely 4 g of acetaminophen may cause severe liver injury in patients with underlying alcohol consumption or with poor food intake. Acetaminophen toxicity is reviewed in detail elsewhere in this issue. Drug-induced hepatic failure has a particularly poor prognosis, with rare spontaneous survival after encephalopathy occurs.

Fulminant hepatic failure typically affects young individuals who had previously been in good health and, before the availability of liver transplantation, was associated with 80% to 90% mortality, especially in patients who progressed to grade 3 or 4 hepatic encephalopathy. With successful transplantation, more than 90% of patients survive [3]. Although many factors contribute to the mortality, the terminal event is typically brainstem herniation from progressive brain edema. Hepatic encephalopathy is divided into four stages, with coma in stages 3 and 4 subdivided into four grades (Tables 2 and 3). Clinical evidence of intracranial hypertension includes

Table 1
Etiology of fulminant hepatic failure in the United States

	N	%	% Spontaneous survival (excludes death or transplantation)
Acetaminophen	60	20	60
Hepatitis non-A-E	44	15	10
Drug-induced	33	12	10
Hepatitis B	30	10	15
Hepatitis A	21	7	35
Miscellaneous ^a	122		
Total of series	295		

^a Includes: Wilson's disease, acute fatty liver of pregnancy, Budd-Chiari syndrome, mushroom intoxication, ischemic injury, autoimmune hepatitis, and rare viruses (herpes, adenovirus).

From Schiodt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999;5:29-34; with permission.

Table 2
Stages of hepatic encephalopathy

Stage 1	Slowing of consciousness
Stage 2	Drowsiness
Stage 3	Confusion, reactive only to vocal stimuli
Stage 4	Comatose

hyperventilation, opisthotonus, hyperpronation-adduction of the arms, cardiac arrhythmias, myoclonus, seizures, and poorly reactive pupils.

Patients with acute liver failure initially present with vague and nonspecific symptoms, such as anorexia and malaise, which are suggestive of a viral illness. Once jaundice occurs, liver function tests typically reveal massive elevations in aspartate aminotransferase and alanine aminotransferase, elevated bilirubin, significant elevation in the prothrombin time, and, sometimes, metabolic acidosis. If acetaminophen overdose is suspected, acetaminophen levels should be obtained and the patient should receive intravenous *N*-acetylcysteine.

These patients must be hospitalized and monitored closely in a specialized liver unit for frequent surveillance of their liver function tests, prothrombin time, complete blood count, arterial blood gases, blood sugars, electrolytes, and neurologic status. They should receive enteral lactulose. The patient developing stage 3 or 4 encephalopathy should be intubated for airway protection to prevent pulmonary aspiration. The patient should be aggressively monitored for hemodynamic instability. An intracranial pressure monitor should be placed if the patient's neurologic status cannot be followed clinically to assess accurately progressive brain swelling and cerebral perfusion pressures [4]. Standard therapies for cerebral edema (including hypothermia) should be used. If cerebral hypoperfusion becomes sustained and refractory, the patient may no longer be considered a liver transplant candidate because of irreversible brain injury. Liver transplantation is currently the best therapeutic option for acute irreversible liver failure. The criteria for liver transplantation include serum factor V level less than 30%, pH less than 7.30, international normalized ratio (INR) greater than 6.5, stage 3 or 4 encephalopathy, and lack of response to medical therapy within 24 to 48 hours (Box 1).

Table 3
Grading of coma in stages 3 and 4 hepatic encephalopathy

Grade 1	Reactivity to vocal stimuli
Grade 2	Absence of reactivity to vocal stimuli, but with a coordinated response to painful stimuli
Grade 3	Absence of reactivity to vocal stimuli, but with an incoordinated response to painful stimuli
Grade 4	Brain death

Box 1. Criteria for transplantation for acute liver failure

Kings College Criteria [5]

Acetaminophen toxicity

pH <7.30 (after hydration and regardless of degree of encephalopathy)

or

INR >6.5

creatinine >3 mg/dL

Encephalopathy grade III–IV

Nonacetaminophen etiology

INR >6.5 irrespective of degree of encephalopathy

or three of the following five criteria

Age <10, >40

Etiology: non-A–E hepatitis, drugs

Duration of jaundice before encephalopathy >7 days

INR >3.5

Serum bilirubin >17.5 mg/dL

Clichy criteria [6]

Factor V <20% (age <30 years) or <30% (age >30 years)

Confusion or coma

Early referral to a liver transplantation center is essential because (1) it is difficult to predict which patients will recover spontaneously; (2) deterioration can occur suddenly; (3) the chance of receiving a liver transplant increases with early placement on the waiting list; and (4) once brainstem herniation has occurred, patients are not salvageable by any means, including liver transplantation.

Hepatic support

Because of a severe shortage of human donors, many patients with acute liver failure die while waiting for a suitable donor organ. Patients should be referred to centers that cannot only perform liver transplantation, but can support such patients until a donor liver becomes available. In addition to standard medical support, several strategies are being developed for temporary hepatic support, including artificial liver support devices, bioartificial livers, hepatocyte transplantation, and extracorporeal liver perfusion.

Artificial liver support systems

Although some studies have suggested that charcoal hemoperfusion systems have a survival advantage for certain causes of fulminant hepatic failure, most patients do not seem to benefit [7]. Other artificial liver support systems have included dialysis-like systems coupled with absorbent

technology, where dialysis fluid containing charcoal and a cation exchange resin is used to bind toxic substances in the blood. A pilot study showed that this system was well tolerated and could produce biochemical improvements in acute liver failure, but did not retard the progression to terminal brain swelling. In the molecular absorbents recirculating system, the dialysis system contains albumin impregnated in the polysulphone membrane and has a dialysate enriched with albumin to facilitate removal of toxic metabolites [8]. In the microsphere-based detoxification system, plasma is recirculated at high flow rates with the entire flow exposed to particle-size absorbents that provide a large surface area for absorption [9].

Bioartificial liver support systems

Another approach consists of a bioartificial liver, wherein plasma, obtained by a centrifugal plasma separator, is perfused through microcarrier-bound porcine hepatocytes [10]. In the extracorporeal liver assist device, blood is perfused through hollow fiber membranes surrounded by cells of a human tumor hepatocyte line [11].

Hepatocyte transplantation

More recently, hepatocyte transplantation has been successfully used to treat certain metabolic disorders, even when associated with acute liver failure [12]. The number of cryopreserved hepatocytes required to achieve success, however, may limit the use of this approach.

Extracorporeal liver perfusion

Extracorporeal liver perfusion overcomes the following problems associated with the previous approaches: inability to support all the hepatic functions, and inability to provide sufficient hepatic support to overcome the derangement from fulminant hepatic failure. In extracorporeal liver perfusion, a centrifugal pump and tissue oxygenator pumps blood derived from the femoral vein through an extracorporeal circuit, containing human or porcine livers, and then returns the blood to the patient through the jugular or axillary vein. This approach has successfully provided biochemical and neurologic improvement in patients, and can successfully provide a bridge to liver transplantation [13].

The limiting factor with porcine livers is vascular rejection, which occurs 2 to 4 hours after initiating perfusion, because of preformed human antibodies to porcine endothelium. Because of a severe donor organ shortage, strategies have been developed to overcome the early rejection associated with pig-to-primate xenotransplantation [14]. An exciting approach is the development of pigs that are transgenic for human complement regulatory proteins. In this situation, complement is not activated in pig endothelium and early rejection may be avoided. Transplantation of kidneys from transgenic pigs to nonhuman primates extends graft survival from hours to weeks when compared with kidneys from nontransgenic pigs.

Liver transplantation for chronic liver disease

Complications of cirrhosis

Cirrhosis arises from hepatocellular or cholestatic liver disease. Both groups have further subclassifications (Table 4). Although all etiologies share common features of liver failure when advanced, unique aspects of each etiology influence management during and following liver transplantation.

Liver transplantation is also indicated for patients with certain metabolic diseases that can present with liver failure without cirrhosis (Table 5). This occurs more commonly in the pediatric population, but can occasionally

Table 4
Cirrhosis and liver transplantation

Disease indication for liver transplantation; Special considerations for liver transplantation (OLT)

Hepatocellular diseases

Chronic hepatitis

Hepatitis B	HBV-DNA negative
Hepatitis D	Co- or superinfects hepatitis B
Hepatitis C	Exclude alcohol
Autoimmune	Exclude bone disease
Drug-induced	Examples: nitrofurantoin, alpramethyldopa

Steatohepatitis

Alcohol	Abstinence and social support
Obesity	Increasing prevalence of cirrhosis
Drug-induced	Example: amiodarone

Vascular disease

Chronic Budd-Chiari syndrome	Decompressive surgery Exclude myeloproliferative syndrome, hypercoagulable state
------------------------------	--

Inborn errors of metabolism

Hemochromatosis	Cardiac involvement
α_1 -Antitrypsin deficiency	Lung disease
Wilson's disease	OLT for acute disease not amenable to medical therapy
Glycogen storage disease type I/III	Can present in early adulthood

Cholestatic diseases

Disease of intrahepatic bile ducts

Biliary atresia	Kasai procedure may offer relief for a few years before
Primary biliary cirrhosis	Bone disease can be especially problematic after OLT
Drug-induced disease	Examples: chlorpromazine, tolbutamide
Familial cholestasis	Byler's syndrome, arteriohepatic dysplasia
Cystic fibrosis	Insipissated bile syndrome leading to cirrhosis

Disease of extrahepatic bile ducts

Primary sclerosing cholangitis	Secondary cholangiocarcinoma may contraindicate OLT
Secondary biliary cirrhosis	Requires Roux-en-Y anastomosis at OLT

Abbreviation: OLT, orthotopic liver transplant.

Table 5
Liver abnormalities without cirrhosis

<i>Congenital abnormalities</i>	
Urea cycle enzyme deficiency	Severe hyperammonemia may cause neurologic deficits
Homozygous hypercholesterolemia	Status of coronary arteries pre-OLT
Primary hyperoxaluria type I	Renal transplantation
Familial amyloidotic polyneuropathy	Assess cardiac status
<i>Developmental abnormalities</i>	
Polycystic liver disease	OLT indicated for symptoms
Caroli's disease	Chronic biliary sepsis

Abbreviation: OLT, orthotopic liver transplant.

extend into young adulthood. Some congenital abnormalities (urea cycle enzyme deficiencies, familial hypercholesterolemia, and familial amyloidosis) can present with so severe extrahepatic manifestations that liver transplantation is recommended in the absence of hepatic disease. Finally, miscellaneous chronic disorders may require transplantation in the absence of both cirrhosis and hepatic failure.

Pathophysiology of chronic liver disease

Advanced liver disease results in two cardinal pathophysiologic abnormalities: hepatocellular failure and portal hypertension. Portal hypertension is rarely a clinical problem in acute liver failure, but can cause complications in cirrhotics even when hepatocellular function is relatively well preserved. The importance of these two factors is recognized in the Child-Turcotte-Pugh classification, a prognostic tool in patients with cirrhosis (Table 6).

Portal hypertension

Portal pressure increases because of increased hepatic vascular resistance and increased portal venous inflow. The anatomic site of the increased intrahepatic vascular resistance varies according to the etiology of the cirrhosis [15]. The hepatic sinusoids are the critical site for alcoholic cirrhosis. Once a critical level of portal hypertension is reached (hepatic venous pressure

Table 6
Prognosis in cirrhosis: Child-Turcotte-Pugh classification

Points	1	2	3
<i>Reflecting portal hypertension</i>			
Ascites	None	Controlled	Not controlled
Hepatic encephalopathy	None	Controlled	Not controlled
<i>Reflecting hepatocellular failure</i>			
Bilirubin (mg%)	0–2	2–3	>3
Prothrombin time (seconds prolonged)	0–3	3–6	>6
Albumin (g%)	>3.5	2.8–3.5	<2.8

Minimum score: 5; maximal score: 15.

Child-Turcotte-Pugh class: A: 5–6; B: 7–9; C: ≥ 10.

gradient of 10–12 mm Hg, defined as the pressure gradient between the portal vein and the hepatic vein), portosystemic collaterals form to decompress the portal system. Portal hypertension is sustained by the development of increased portal venous inflow from a generalized hyperdynamic circulation in both acute and chronic liver failure.

Primary liver cancer

About 80% of people with hepatocellular carcinoma (HCC) have cirrhosis. Chronic hepatitis B or hepatitis C virus infection also increases the risk of developing HCC, with an annual incidence of HCC of 3% to 9% with these infections [16]. Aflatoxins produced by a mold that is a contaminant of nuts (most commonly peanuts), grains, and beans have also been implicated as a major risk factor for HCC. Most HCCs are first suspected based on a screening abdominal ultrasound, and confirmed by CT or MRI. Serum alpha fetoprotein is a useful diagnostic marker, but is not very specific. It is often used to screen patients with cirrhosis from chronic hepatitis B or chronic hepatitis C. A rising serum alpha fetoprotein concentration in someone with chronic liver disease suggests the development of HCC.

HCC is curable by surgery only if the cancer is small and the patient has adequate hepatic reserve. In patients with hepatic insufficiency or severe portal hypertension, liver transplantation may also be curative for the cancer and the underlying hepatic disorder. Surgery or liver transplantation is contraindicated if there is evidence of metastases, in which case liver-directed therapies (transarterial chemoembolization or radioembolization) may be beneficial.

Currently, patients with HCC who require transplantation undergo evaluation and listing through the standard process (see later); however, these patients often have normal hepatic synthetic function. Upgrades within the UNOS organ allocation scheme using the Model for End Stage Liver Disease (MELD) scheme may be necessary to procure timely liver transplantation. The currently accepted criteria are the Milan criteria [17], where T1 and T2 lesions allow MELD score upgrades, and achieve over 80% 2-year recurrence-free survival after transplantation. Even with these upgrades, the current waiting times suggest the need for liver-directed therapy as an oncologic bridge to transplantation, although this has not been shown to reduce posttransplant recurrence.

Cholangiocarcinoma is now another potential indication for liver transplantation. The preferred situation is patients with primary sclerosing cholangitis who have cytologic evidence of intrahepatic carcinoma. Transplantation is performed after neoadjuvant therapy. Recurrence rates are substantially reduced compared with the historical experience [18]. Secondary liver cancers, such as neuroendocrine tumors and salivary gland tumors, may be treated by liver transplantation. Such lesions need to be low-grade malignancies without extrahepatic spread to diminish the risk of recurrence after transplantation.

Recipient evaluation

Thorough evaluation of a candidacy for liver transplantation includes assessment of the need, urgency, and technical feasibility of orthotopic liver transplant. The acuity and extent of the investigation is frequently determined by the severity of liver disease. The evaluation is streamlined and accelerated in patients with fulminant hepatic failure because they require relatively urgent therapeutic decisions. Recipient evaluation includes the following four areas.

Etiology of liver disease

This aspect requires an adequate history, physical examination, and laboratory testing (**Box 2**), including radiologic imaging of the liver and endoscopic evaluation of the gastrointestinal tract. A liver biopsy, obtained either percutaneously or by the transjugular route in patients with ascites and severe coagulopathy, can provide a definitive diagnosis that may be critical in selected patients with acute liver failure and for other patients in whom alcoholic hepatitis is suspected.

Complications of cirrhosis

Several complications of cirrhosis signal the need to proceed with liver transplantation and require selective diagnostic tests, as delineated in **Box 3**.

Exclusion criteria (contraindications)

Although liver transplantation is not absolutely contraindicated at any specific chronologic age, evaluation of physiologic age requires a thorough clinical assessment, including evaluation of cardiac function. Obese and diabetic individuals are at significant risk of atherosclerotic vascular disease that requires full cardiovascular evaluation. Although noninvasive cardiac testing may be adequate in the younger, otherwise healthy candidate, this is insufficient for higher-risk patients (**Table 7**).

Box 2. Blood tests to assess etiology of liver disease

- Hepatitis B, HBV-DNA, HBeAg, anti-HBe, and anti-Delta Abs
- Hepatitis C, HCV-RNA, HCV genotype
- Autoimmune: Anti-smooth muscle Ab (ASMA), antinuclear Ab (ANA), antimitochondrial Ab (AMA)
- α_1 -antitrypsin level and phenotype
- Wilson: ceruloplasmin, 24-h urine copper, hepatic copper
- Hemochromatosis: iron saturation, ferritin, HFE gene test
- Blood group: for listing purposes

Abbreviation: Ab, antibody.

Box 3. Testing to assess the complications of liver disease

- Arterial blood gases: to exclude hypoxemia-hepatopulmonary syndrome
- Liver imaging: to exclude HCC
- Serum alpha fetoprotein, Ca19-9: to exclude HCC, cholangiocarcinoma
- Doppler ultrasound: to exclude portal vein thrombosis
- Upper gastrointestinal endoscopy: to assess portal hypertension
- Bone densitometry: selected patients
- Neuropsychologic testing: selected patients

Coexisting medical conditions need to be excluded. Uncontrolled sepsis outside the biliary tract constitutes an absolute contraindication to liver transplantation. Metastatic hepatobiliary or extrahepatic malignancies also constitute absolute contraindications. For extrahepatic cancers, a waiting period of 5 years after treatment of a solid organ tumor and 2 years after treatment of a hematologic malignancy is recommended. Although HIV infection is no longer a contraindication, the presence of AIDS is a contraindication to transplantation, because posttransplant immunosuppression accelerates the course of AIDS. Irreversible brain damage and multiorgan failure also precludes liver transplantation.

Psychosocial assessment

It is important to predict the ability of the candidate to exhibit discipline and responsibility after transplantation. Assessment of the patient's life style, psychologic stability (including his or her perception of disability),

Table 7
Testing to exclude contraindications

Infectious disorders	HIV, syphilis, EBV, cytomegalovirus, toxoplasmosis
Malignancy	Colonoscopy in primary sclerosing cholangitis (ulcerative colitis) ERCP in primary sclerosing cholangitis (cholangiocarcinoma) In HCC: bone scan, lung CT (metastatic work-up) Screening (colon, breast, cervical, prostate cancer)
Cardiopulmonary status	Chest radiograph, electrocardiogram, two-dimensional-echocardiogram (routine) Thallium stress test, coronary angiography (patients at risk) Pulmonary function tests

Abbreviations: CT, computerized tomography; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.

and extent of family support require interaction with psychiatric and social work support services. This evaluation is critical for patients with alcoholic liver disease. The ability to abstain from alcohol after transplantation is predicted by the ability to abstain before transplantation for at least 6 months, relatively stable employment history, and a family and friend support structure. Drug abuse needs to be explicitly discussed. Emergency psychiatric assessment is required for acute hepatic failure from ingestion of acetaminophen during a suicidal attempt; a psychiatric interview should occur before the patient develops altered mentation. If the patient already has altered mentation, the team has to rely on the prior medical and psychiatric history, including previous suicidal attempts, and a family interview to reach a decision.

Selection criteria and listing process

The decision to proceed with transplantation requires careful assessment of the etiology and stage of liver disease, complications of cirrhosis, potential contraindications, and a comprehensive psychosocial evaluation. A multidisciplinary review board dispassionately evaluates the pros and cons of each candidate to reach a rational decision. Input from consulting physicians, psychiatrists, ethicists, and social workers is critical. Each candidate has an advocate who presents his or her case to the selection committee. The vote to proceed must be unanimous.

The patient has to meet minimal listing criteria for placement on the waiting list (Child-Turcotte-Pugh score of at least 7 for most causes of cirrhosis). Once approved for listing, the patient is prioritized according to the MELD score. This score, based on objective laboratory values, predicts the 3-month mortality of patients awaiting liver transplantation. The MELD score incorporates serum creatinine, serum bilirubin, and INR (Table 8).

Clinical management while awaiting liver transplantation

With increasing waiting times, maintaining the patient in an acceptable medical condition to undergo successful liver transplantation is challenging. Prophylactic measures and therapeutic interventions may be needed to deal with numerous potential intervening complications.

Table 8
Model for End-Stage Liver Disease

MELD score	$= 0.957 \times \text{Log}_e(\text{creatinine mg/dL})$ $+ 0.378 \times \text{Log}_e(\text{bilirubin mg/dL})$ $+ 1.120 \times \text{Log}_e(\text{INR})$ $+ 0.643$
------------	--

Abbreviations: INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease.

Timing of liver transplantation

A sound knowledge of the natural history of liver disease is essential for the timing of transplantation. Hepatic complications typically upgrade the priority status for transplantation but downgrade the surgical prognosis. In acute liver failure, prognostic criteria help assess the need for urgent liver transplantation. In patients with chronic liver disease, the prevention and management of potential complications requires diligent and comprehensive clinical care.

Prophylaxis of complications

Patients on the waiting list are at risk of developing HCC. Screening with abdominal ultrasound and alpha fetoprotein level determination every 6 months is generally performed. Screening upper endoscopy, to exclude the presence of medium to large esophageal varices, is also recommended, because patients with such varices may benefit from prophylaxis with β -blocker therapy.

Therapy of complications

The rationale for each therapy is beyond the scope of this article and the reader is referred to standard references [15,19,20]. Each of the four major complications has a management protocol (Box 4). The development of one complication, however, can trigger additional complications. Gastrointestinal hemorrhage and infection can aggravate liver and renal abnormalities, whereas intractable ascites impairs respiratory function and aggravates malnutrition. Hepatic encephalopathy can result in aspiration pneumonia and may require prophylactic tracheal intubation. Fluid overload in the setting of renal failure and severe hypoalbuminemia requires extracorporeal measures, such as continuous venovenous hemofiltration. Patients require extensive and intensive support to overcome these problems.

Recipient operation

When a suitable donor is identified, a rapid evaluation of the recipient is performed to exclude potential contraindications (eg, infectious, cardiovascular) that may have arisen during the waiting period. Please refer to the appropriate sources for donor and anesthetic issues. The ensuing section highlights the surgical aspects of liver transplantation to assist all members of the multidisciplinary transplant clinical team.

Standard surgical technique

The recipient operation consists of total hepatectomy of the native liver followed by implantation of the donor liver. The native hepatectomy can be technically difficult, especially in patients with previous upper abdominal

operations and severe portal hypertension. The ligamentous attachments of the liver are divided, followed by skeletonization of the hilar structures (bile duct, hepatic artery, and portal vein) to prepare for implantation of the new liver. The inferior vena cava (IVC) is encircled above and below the liver to achieve full vascular control. Committing the patient to transplant, the bile duct and hepatic artery are divided. Vascular clamps are placed on the portal vein and the IVC below and above the liver, and the liver is removed by transecting the portal vein and the IVC. The retrohepatic IVC is removed with the liver.

At this point, hemostasis is achieved as well as possible. This may be difficult in patients with severe coagulopathy or portal hypertension. The donor liver is surgically prepared for implantation on the back table, including cholecystectomy, and then brought onto the operative field. Anastomoses are constructed between the donor liver and recipient patient in the following sequence: suprahepatic IVC, infrahepatic IVC, and portal vein anastomosis. In the case of a thrombosed or inadequate portal vein, a donor iliac vein conduit is anastomosed preferably to the confluence of the splenic and superior mesenteric veins or alternatively to any patent branch of the portal venous system including the superior mesenteric veins. Once the portal vein is anastomosed, the clamps are removed in sequence and the liver is perfused with portal venous inflow.

Venous-venous bypass is occasionally used, before completion of the hepatectomy, to decompress the splanchnic venous system and ensure venous return from the lower extremities [20]. Some centers use venous-venous bypass, and other centers never use it, but most centers use venous-venous bypass in selected patients, especially for a difficult hepatectomy (hemorrhage, cardiovascular instability) (Box 5). Venous-venous bypass requires cannulation of a lower extremity vein (typically the saphenofemoral vein); an upper extremity or neck vein; and the portal vein. This circuit allows decompression of the portal venous system and maintenance of cardiac preload during the anhepatic phase.

The hepatic artery is typically connected to the recipient hepatic artery at the junction of the gastroduodenal artery. In 15% to 20% of cases, the donor liver has arterial anatomic variants, which require arterial reconstruction on the back bench to create a single inflow channel. Occasionally, the inflow from the recipient hepatic artery is inadequate because of inadequate systemic flow or abnormal arterial anatomy in the recipient. Donor iliac arteries are routinely harvested during the donor procedure. These arteries can be used to construct a conduit between the recipient aorta and the donor hepatic artery or celiac axis.

Once the liver is arterialized and the hepatic artery demonstrates satisfactory flow, hemostasis is achieved, and the bile duct is reconstructed using an end-to-end choledochocholedochostomy. Several variations of this anastomosis are used. In the past stenting of this anastomosis was routine. In many centers, the use of a T-tube has been questioned because of a significant

Box 4. Treatment of complications of cirrhosis

Variceal hemorrhage

Initial hemostasis

- Pharmacologic therapy
 - Vasopressin (0.1–0.4 U/min) and nitroglycerin (start with 1 µg/kg/min IV)
 - Octreotide (100 µg bolus, 50 µg/h infusion [still unproved when given alone])
- Endoscopic therapy
 - Variceal band ligation
 - Fundic varices not amenable to endoscopic therapy in the United States
- Mechanical tamponade
 - Sengstaken-Blakemore tube

Prevention of early rebleeding

- Octreotide infusion for 5 days
- Treatment of bacterial translocation: norfloxacin, 400 mg/day

Maintenance therapy

- Pharmacologic therapy
 - Propranolol, to reduce portal pressure by 20%, start with 20 mg bid (requires hepatic vein catheterization) or
 - Maximal dosage that reduces heart rate by 25% from baseline or not <55 beats/min
 - If portal pressure reduction not attained, add isosorbide mononitrate, 5 mg bid
- Endoscopic therapy
 - Continue variceal band ligation until eradication of varices (achieved with four to five sessions in 40%–50% of patients)

Failure of therapy

- *Shunt surgery*, especially distal splenorenal shunt
 - For patients with good liver function (Child-Pugh score of 5–7 and no ascites)
- Transjugular intrahepatic portal-systemic shunt
 - Rescue therapy, for patients with poor liver function

Hepatic encephalopathy

1. Correct precipitating event
 - Cleansing enemas for gastrointestinal bleeding
 - Volume expansion/electrolyte correction
 - Treatment of infection (without aminoglycosides)
 - Antagonism of sedatives (flumazenil, nalcron)
2. Diet
 - Protein intake should be at least 0.75–1 g/kg

3. Nonabsorbable disaccharides
Lactulose, po 20–30 mL q 8–12 h
4. Zinc sulfate, 300 mg q 12 h
5. Antibiotics on intestinal flora
Neomycin (3–6 g/day) for short periods
Metronidazole, start at 250 mg bid
6. In stage III-IV encephalopathy Endotracheal intubation to prevent aspiration

Ascites

1. Diet and fluid balance
Bed rest and low-sodium diet (2–4 g/d)
Fluid restriction (1 L/day) for serum sodium <130 mEq/L
2. Diuretics
Spironolactone (100–400 mg/d) alone or with furosemide (20–160 mg/day)
Carefully monitor for diuretic complications
Renal impairment
Hepatic encephalopathy
Hyperkalemia with renal failure (spironolactone)
3. Large-volume paracentesis
Indicated for tense ascites that impairs respiration, or refractory ascites
Albumin administered after paracentesis (6 g/L removed)
4. *Transjugular intrahepatic portosystemic shunt*
Poor outcome (worsening liver failure) in patients with Child class C cirrhosis
5. *Hepatorenal syndrome*
Ensure volume expansion with central pressure monitoring

Spontaneous bacterial peritonitis

1. Choice of antibiotics
Initial therapy with cefotaxime, 3–6 g/d (or equivalent) until culture results known
Repeat paracentesis after 48 hours to ensure response (>50% decrease of polymorphonuclear leukocytes in ascitic fluid)
2. Culture-negative neutrophilic ascites
Repeat paracentesis critical
3. Prevention of renal failure
Discontinue diuretics until satisfactory microbiologic response
Prophylaxis, several regimens proposed
Norfloxacin, 400 mg/d; bactrim, 5 d/wk; ciprofloxacin, 1/wk

Box 5. Potential indications for venous-venous bypass

1. Severe retroperitoneal collateralization
2. Poor preoperative renal function
3. Hypotension following test clamping of the vena cava despite adequate volume loading
4. Intestinal or mesenteric edema
5. Fulminant hepatic failure

risk of biliary leaks following removal of the T-tube and other technical problems associated with T-tubes [21]. If the recipient bile duct is not appropriate for end-to-end reconstruction, a Roux-en-Y choledochojejunostomy is performed in standard fashion, with or without internal stenting (Box 6).

*Alternative techniques**Piggyback procedure*

The recipient hepatectomy can be altered to leave the recipient retrohepatic IVC in situ. The donor IVC is then anastomosed side-to-side to the recipient IVC and the remaining structures are anastomosed in standard fashion. This technique is used to avoid the need for venous bypass during LDLT.

Split liver procedure

The use of split livers has become a recent option for selected donor livers for most liver recipients. The liver is typically split along the falciform ligament separating the left lateral segment (Couinaud segments II and III) from the remaining liver. The main hilar vascular and biliary structures are retained with the right side of the liver. The left lateral segment is typically transplanted into a child and the remaining liver transplanted into an adult. The surgery for a split liver is identical to that for a whole liver, except

Box 6. Indications for choledochojejunostomy

1. Donor-recipient bile duct size discrepancy
2. Diseased recipient bile duct
 - Secondary biliary cirrhosis
 - Primary sclerosing cholangitis
 - Choledocholithiasis
 - Biliary atresia
3. Presence of biliary duct malignancy
4. Poor blood supply to recipient bile duct
5. Inability to pass biliary probe through ampulla

for the need to secure hemostasis at the cut hepatic surface and to check carefully for biliary leaks at this surface. Split liver transplants, when performed on properly selected recipients using suitable donor livers, has survival results comparable with whole livers, but has a slightly higher rate of surgical complications [22,23].

Postoperative care

Major considerations in the immediate postoperative period include liver function, postoperative bleeding, and general considerations.

Liver function

A disastrous complication of liver transplantation is primary nonfunction. Primary nonfunction is differentiated from graft dysfunction, which encompasses a spectrum ranging from mild graft dysfunction, manifested by elevated liver enzymes and poor early hepatic synthetic function, to severe dysfunction, manifested by prolonged synthetic dysfunction, hemodynamic instability, and associated multiorgan dysfunction [24]. Severe graft dysfunction and primary nonfunction require consideration of urgent retransplantation, whereas mild-to-moderate graft dysfunction requires close observation and supportive therapy. Indicators of good early graft function include normalization of prothrombin time, and factor V and transaminase levels. In addition, clearance of lactic acidosis, awakening from the anesthetized state, and good renal function provide further affirmation of liver function (Box 7).

Postoperative bleeding

Significant coagulopathy can be present following hepatic revascularization attributed to fibrinolysis, heparin-like effect, thrombocytopenia, and coagulation factor deficiencies. Usually, coagulopathy is reversed by the time of abdominal closure with a functioning graft. If ongoing bleeding, despite correction of coagulopathy and rewarming of the patient, is suspected,

Box 7. Favorable signs regarding hepatic function in the immediate postoperative period

1. Hemodynamic stability
2. Awakening from anesthesia
3. Clearance of lactate
4. Resolution of hypoglycemia
5. Normalization of coagulation profile
6. Resolution of elevated transaminases

especially if hemodynamic instability and oliguria are present, the patient should undergo reoperation to evacuate a hematoma and to identify and stem the ongoing bleeding. Postoperative bleeding is high in the differential diagnosis of early postoperative hypotension and oliguria.

General considerations

Hemodynamic stabilization is clinically assessed by adequate organ and tissue perfusion. Patients with cirrhosis typically exhibit hemodynamic parameters consistent with those of a septic patient, including high cardiac output and low systemic vascular resistance. These hemodynamic conditions can persist for several weeks following transplantation, and may require vasoconstrictive therapy. Pulmonary management consists of standard ventilatory support. Pulmonary complications are common in the postoperative period because of the large surgical incision, the debilitated state of the patient, and frequent pleural effusions. Pulmonary care is highly important following extubation.

Laboratory testing includes careful attention to the serum levels of glucose and electrolytes. In addition to attention to sodium and potassium levels, magnesium levels are typically low and magnesium supplementation is required. The ionized calcium level should be frequently determined and normalized. The transaminase levels, prothrombin time, and factor V levels should normalize during the first 24 hours. A baseline Doppler ultrasound to assess patency of the hepatic artery should be performed within the first 24 hours after transplantation.

Liver function test abnormalities

Liver function test abnormalities may consist of elevations in liver transaminases, suggestive of hepatocellular necrosis, or elevation of alkaline phosphatase and bilirubin, suggestive of cholestasis. These two patterns of liver function abnormality are not mutually exclusive and can occur simultaneously. The differential diagnosis of abnormal liver function tests include graft dysfunction, vascular or biliary surgical complications, immunologic complications (graft rejection), infectious complications, and recurrence of native disease (Box 8).

Graft dysfunction

Graft dysfunction ranges from mild to severe. Mild dysfunction is manifested by a significant rise in the serum transaminases postoperatively (above 2500 IU) from preservation injury. A second peak in transaminases within 24 hours may occur secondary to reperfusion injury. If the transaminase levels continue to rise beyond 12 to 24 hours after transplantation, a complete evaluation should be performed, including assessment of mental

Box 8. Causes of hepatic dysfunction after liver transplantation

Immediate

1. Primary allograft nonfunction
2. Primary allograft dysfunction
3. Hepatic artery thrombosis
4. Portal vein thrombosis
5. Hepatic vein and caval thrombosis
6. Biliary tract obstruction or leak

Delayed

1. Rejection
2. Infection
3. Biliary tract obstruction
4. Recurrent disease

status, coagulation profile, renal function, and hemodynamic stability (Box 9).

Severe liver dysfunction or primary nonfunction must be differentiated from technical vascular complications including hepatic artery thrombosis, portal vein thrombosis, and hepatic congestion secondary to venous outflow obstruction. Preservation injury is generally associated with improving mental status and a stable or improving prothrombin time that is easily correctable. Contrariwise, primary nonfunction is manifested by progressive deterioration of mental status, a worsening coagulation profile, renal dysfunction, and hemodynamic instability. The treatment of severe hepatic dysfunction is primarily supportive. Intravenous prostaglandin E₁ has been shown to be beneficial [25]. In cases of moderate liver dysfunction, the transaminases normalize over time, as do the coagulation parameters, even though these patients become severely cholestatic during the recovery period.

Box 9. Signs of primary liver graft nonfunction

1. Failure to regain consciousness
2. Hemodynamic instability
3. Poor quality and quantity of bile
4. Increasing prothrombin time
5. Renal dysfunction
6. Rise in serum transaminases and bilirubin
7. Acid-base imbalance
8. Persistent hypothermia

Vascular complications

Hepatic artery thrombosis presents with various liver test abnormalities, including very subtle elevations in the serum transaminases, and may not be diagnosed in the early postoperative period and manifest later with biliary complications, such as bile leaks, bilomas, liver abscesses, and biliary strictures (Box 10). An abnormal trend in liver function tests should be investigated immediately with Doppler ultrasound and, if the hepatic arterial signal is not clearly seen, a hepatic arteriogram and radiologic or operative intervention should be performed. Retransplantation may be necessary, especially if liver function is severely compromised in the early postoperative period. Hepatic artery thrombosis is usually related to technical complications. Optimal flow should be ensured during implantation, even using quantitative measurements, to avoid this complication [26].

Portal venous thrombosis is uncommon, but can occur in the setting of significant portal vein stenosis or previous portal vein thrombosis in the recipient, especially in the pediatric recipient. Typically, severe elevations in the serum transaminase levels occur early postoperatively. Ascites is a manifestation of delayed portal vein thrombosis. Also, acute portal hypertension manifested by variceal bleeding should alert the clinician to possible acute portal vein thrombosis. In the acute setting, thrombectomy should be attempted to try to save the graft, although retransplantation may be necessary.

Venous outflow obstruction causing a Budd-Chiari–like congestion of the liver can occur. In the early postoperative period, a significant elevation in the transaminase levels results from the acute congestion, requiring surgical correction, whereas delayed manifestations consist primarily of ascites and manifestations of portal hypertension, which may be addressed by endovascular techniques.

Biliary tract complications

Anastomotic biliary leaks can occur early postoperatively, resulting in localized or generalized peritonitis. Biliary output from the drains and elevation in serum bilirubin disproportionate with the elevation of the other

Box 10. Manifestations of hepatic artery thrombosis after liver transplantation

1. Elevation of the serum transaminases and bilirubin
2. Fulminant hepatic failure
3. Sepsis with hepatic abscesses or gangrene of the liver
4. Biliary anastomotic disruption
5. Biliary tract strictures

liver function tests raise this diagnostic possibility. Early leaks are best treated by reoperation and revision to a Roux-en-Y choledochojejunostomy. Localized leaks may be treated with endoscopic retrograde cholangiopancreatography (ERCP) and stenting.

Delayed complications include bile duct anastomotic strictures and intrahepatic biliary strictures, sometimes related to hepatic artery thrombosis. These strictures are usually dilated and stented at ERCP. When these interventions fail, biliary reconstruction with a Roux-en-Y choledochojejunostomy may be necessary. Dysfunctional motility of the bile duct and Sphincter of Oddi may cause functional obstruction without mechanical obstruction [27]. These problems manifest later in the postoperative period. Also, biliary casts and stones can form, especially with prolonged ischemia, and cause biliary obstruction requiring ERCP intervention.

Rejection

Rejection can occur in the first few days after transplantation, especially if induction immunosuppressive therapy is not used. The liver function test abnormalities can be hepatocellular or cholestatic. Diagnosis is made by liver biopsy because the clinical signs and symptoms of rejection (including fever, elevation of the bilirubin or transaminase levels, malaise, and increased ascites) are highly variable, nonspecific, and unreliable.

Acute cellular rejection usually occurs between the fourth and fourteenth day after transplantation and rarely occurs more than 3 months after transplantation. Some patients are asymptomatic, whereas others experience profound symptoms caused by liver allograft failure. The diagnosis of allograft rejection is confirmed by histologic examination of a liver biopsy. Classic histologic findings include a portal infiltrate consisting of mixed inflammatory cells. The presence of eosinophils, lymphocyte-mediated bile duct injury, and endothelialitis can be diagnostic (Table 9).

Table 9
Histologic determinants of acute liver graft rejection

1. Portal infiltrate with mixed inflammatory cells	
2. Bile duct injury	
3. Endothelialitis	
Grading of acute liver allograft rejection—Banff Criteria	
Grade	Criteria
I (mild)	Cellular infiltrate in a minority (<50%) of the portal triads, that is generally mild, and confined within the portal spaces
II (moderate)	Cellular infiltrate, expanding most (>50%) or all of the portal triads
III (severe)	As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

From Demetris AJ, Batts KP, Dhillon AP, et al. Banff schema for grading liver allograft rejection: an international consensus document. *Hepatology* 1997;25:658–63; with permission.

Infection

Abnormal liver function tests secondary to infection most commonly arise from viral infections, including cytomegalovirus hepatitis, and recurrence of previous viral hepatitis. Cytomegalovirus hepatitis is diagnosed by the presence of inclusion bodies with clusters of polymorphonuclear cells. Evidence of tissue invasion is often associated with symptoms of fever, general malaise, and myalgias. The diagnosis is corroborated by shell viral culture, positive antigenemia tests, or polymerase chain reaction. Treatment consists of reduction in immunosuppression and antiviral agents, such as ganciclovir. Bacterial or fungal systemic infections may also result in abnormal liver function tests, usually with a cholestatic pattern. Hepatic abscesses may occur and result in abnormal liver function tests. They typically result from hepatic artery thrombosis, and are diagnosed radiologically. ERCP may be helpful in delineating the extent of biliary duct disruption.

Postoperative care

The specifics of postoperative care are delineated according to the particular postoperative period, including (1) the immediate postoperative, (2) the early postoperative inpatient, (3) the early outpatient, and (4) the long-term outpatient periods.

Immediate postoperative inpatient care

Most of the specifics of the immediate postoperative care were discussed previously. The immediate postoperative period is defined by the postoperative intensive care unit stay. Immunosuppression is usually instituted in this period, and immunosuppression is presently discussed.

Immunosuppression

Induction therapy, in the form of antilymphocyte preparations (MALG, ATG, OKT3), has not been widely used in liver transplantation. Recently, a resurgence of interest in induction therapy has resulted from the introduction of humanized interleukin-2 receptor antibodies. Their role in liver transplantation remains to be elucidated.

Baseline immunosuppression is instituted in the immediate postoperative period. It typically consists of a calcineurin inhibitor, either cyclosporine or tacrolimus, and corticosteroids. Corticosteroids are administered initially as intravenous, and switched to oral prednisone once the patient tolerates oral feedings. Mycophenolate mofetil has largely replaced imuran in kidney and kidney-pancreas transplantation, and is being increasingly used either as a third agent or as an alternative to corticosteroids or even calcineurin inhibitors.

Early postoperative inpatient care

Patients are transferred from the intensive care unit to the transplantation ward when they are extubated and hemodynamically stable. Patients who were debilitated before transplantation often require transfer to acute rehabilitation units to achieve ambulation. Patients who are doing well and who do not need long-term rehabilitation have their diet advanced as tolerated. Standard wound care is administered and the drains are removed if no biliary leak is evident. The presence of large volumes of ascites in the drains should not delay the removal of the drains.

In addition to immunosuppressive agents, prophylaxis is initiated against *Pneumocystis carinii* pneumonia and against cytomegalovirus. Antifungal prophylaxis is achieved with swish and swallow of a nystatin suspension or other similar topical antifungal. Fluconazole or itraconazole is used in the early postoperative period for prophylaxis against systemic fungal infections. These two agents can dramatically increase calcineurin inhibitor levels caused by competition with cytochrome P-450, and the serum calcineurin inhibitor levels need to be closely monitored. Standard antibacterial prophylaxis necessitates coverage of gram-negative and anaerobic agents typically present in bile.

Liver function tests and hematologic and biochemical laboratory values must be closely monitored in the first few days after transplantation. Frequent problems of thrombocytopenia and mild renal dysfunction may require intervention, such as platelet transfusion and optimization of central venous filling pressures, respectively. Common sites of infection following liver transplantation include urinary tract, pulmonary, intra-abdominal, central venous catheter, and wound infections. Fever or leukocytosis requires investigation for possible infection at these sites.

Early postoperative biliary complications typically include an anastomotic leak and potentially a biloma. In the case of increasing leukocytosis, fever, and abdominal pain, with radiographic evidence of a bile leak, percutaneous drainage is required. Early endoscopic therapies (eg, ERCP and stenting) can be performed, even immediately posttransplantation.

Early outpatient care

When the patient tolerates an oral diet and can ambulate, he or she can be discharged and closely followed in an outpatient clinic. Typically, blood work is obtained three times weekly, and the patients are examined weekly, according to a standard, established protocol. At clinic visits the patient's medications are carefully reviewed to avoid errors.

Abnormalities of liver function tests or of other laboratory tests are investigated. The standard evaluation of abnormal liver function tests includes an abdominal ultrasound with Doppler examination to look for hepatic vascular patency, dilatation of the biliary tree, and abnormalities within the hepatic parenchyma, such as liver abscesses. If the abdominal

ultrasound is unremarkable, the next step usually consists of percutaneous liver biopsy to exclude rejection or infection. In the early postoperative period, especially in patients undergoing transplantation for liver diseases other than chronic viral hepatitis, elevation in liver function tests can be treated empirically with steroid boluses without a need for liver biopsy. When needed, liver biopsies can be performed as outpatients and graft rejection can be treated in the outpatient setting. Corticosteroid-resistant graft rejection must be documented by a liver biopsy. Treatment of this consists of a course of antilymphocyte therapies (OKT3, ATG).

If the biopsy does not reveal the cause for the abnormal liver function tests, visualization of the biliary tree is imperative to exclude obstruction. This visualization usually requires ERCP for diagnosis and potentially for intervention. Occasionally, the reason for the elevation of liver function tests remains elusive after these diagnostic tests. With recurrent hepatitis C, a liver biopsy can be misleadingly normal or show only an occasional Councilman's body or apoptosis of hepatocytes despite significantly abnormal liver function tests. In these cases, conservative management and close observation eventually reveal the cause of the abnormal liver function tests. Repeat liver biopsies may be required to establish the diagnosis.

The immunosuppressive agents have side effects. Side effects of the calcineurin inhibitors include nephrotoxicity, neurotoxicity, hyperkalemia, hypomagnesemia, hypertension, and tremor. Tacrolimus also can induce new-onset diabetes, and is more prone to cause abdominal pain and diarrhea than cyclosporine. Both calcineurin inhibitors are metabolized through the cytochrome P-450 system. Their serum levels are increased by erythromycin; antifungal agents, such as ketoconazole, fluconazole, and itraconazole; and calcium channel blockers, such as diltiazem, verapamil, and nicardipine. Drugs that decrease their serum levels include antiepileptic medications, such as phenytoin, phenobarbital, and carbamazepine, and many antituberculosis medications, such as isoniazid, rifampin, and rifabutin. Twelve-hour serum trough levels are measured and monitored closely to guide the dosage of administration.

Azathioprine and mycophenolate mofetil primarily cause leukopenia. The dosage of these agents must be adjusted according to the leukocyte count. The availability of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor has made leukopenia much easier to manage in these patients.

In patients undergoing transplantation for hepatitis B-related chronic liver disease, human hepatitis immunoglobulin (HBIg) preparations are administered in high doses perioperatively. Typically, 10,000 IU are administered intravenously during the anhepatic phase and then daily for 6 to 7 days. Titers of antibody are measured and maintained above 300 IU. Starting 1 week after transplantation, HBIg is administered intravenously weekly at first and then monthly. Eventually, HBIg is administered intramuscularly at monthly intervals to maintain titers above 300 IU. Antiviral

agents have also been used, particularly in patients who were hepatitis B virus DNA positive before transplantation. DNA positivity is a contraindication to liver transplantation unless the patient can be rendered DNA negative with antiviral therapy, such as lamivudine. In patients rendered hepatitis B virus DNA negative with lamivudine, lamivudine-resistant mutants usually arise over time. The combination of HBIg and lamivudine is thought to improve the prophylaxis against recurrence than either agent alone. Although several hepatitis B virus treatments are currently available, further investigation is necessary to identify the optimal posttransplantation therapy.

Live-donor liver transplantation

Overview

During the past decade, the gap between the number of adult patients who need liver transplantation and the number of donated organs has greatly increased. This gap has increased the mean waiting time to undergo liver transplantation and the mortality from complications of end-stage cirrhosis for patients on the waiting list. Attempts to address the inadequate supply of donor organs for transplant have included the use of marginal donors (old age, poor hemodynamics, or chronic viral infection). Living donors have been recently used to address this need.

Use of a living donor developed in the pediatric transplantation more than a decade ago [28]. This option decreases the waiting list mortality, and produces excellent recipient results with a low risk of morbidity and mortality in the donor. This concept was extended to adult LDLT. The LDLT procedure involves transplantation of the right hepatic lobe from an adult donor to the recipient. The first series was presented in the United States in 1998 [29].

Live-donor liver transplant recipient

LDLT is considered for patients likely to experience mortality while awaiting a cadaveric liver donor, for the indications listed in [Box 11](#).

Donor candidacy and evaluation

Potential donors are evaluated by a donor advocate team. Donors must be completely healthy, and have hepatic size and anatomy compatible with right lobe transplantation ([Box 12](#)).

Donor and recipient procedure

The donor procedure consists of a formal right hepatic lobectomy, including intraoperative cholangiogram and ultrasound. Once harvested,

Box 11. Live donor liver transplant candidate recipients

Pre-MELD

Hepatocellular carcinoma (stages T₁ and T₂)

Fulminant hepatic failure

Patients not likely to receive cadaveric organ, with life expectancy less than 6 months

Post-MELD

Hepatocellular carcinoma (exceeding T₂ criteria)

Complications of cirrhosis, low MELD score

Gastrointestinal bleeding

Hepatic encephalopathy

Intractable pruritus

Recurrent cholangitis

Fulminant hepatic failure

Abbreviation: MELD, model for end-stage liver disease.

the right lobe is flushed with preservative solution and vascular reconstruction is completed on the back table to prepare for implantation. The recipient operation involves an IVC-sparing hepatectomy with anastomosis of the donor right-sided vascular and biliary structures to the corresponding

Box 12. Right hepatic lobe donor evaluation

History and physical examination

Psychosocial evaluation (social work, psychiatry)

Laboratory assessment

Complete blood count, chemistry, coagulation profile, thrombophilia screening, viral serologies (HIV, HBV, HCV, and so forth)

Electrocardiogram, chest radiograph

Cardiac stress testing, if indicated

Liver imaging (MRI, MRA, MRV, MRCP, or CT scan/ERCP)

Liver biopsy, if indicated

Family agreement or consent, no compensation or coercion

Abbreviations: CT, computerized tomography; ERCP, endoscopic retrograde cholangiopancreatography; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MRA, magnetic resonance angiography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

recipient structures [30]. LDLT provides an alternative that can reduce the waiting-list mortality in selected patients.

Summary

Currently, approximately 17,000 people await liver transplantation. Quality-of-life studies have shown that most patients have an excellent quality of life following transplantation, with 1-year patient survival at 90% and 5-year patient survival at 75%. De novo malignancies and recurrence of native disease, however, remain as significant challenges. The most significant current hurdle is a dramatic donor organ shortage, although living donor transplants are being increasingly used. The discrepancy between needy recipients and available organ donors necessitates more aggressive and innovative management algorithms for the complications of cirrhosis.

References

- [1] Benhamou JP. Fulminant and sub-fulminant hepatic failure: definition and causes. In: Williams R, Hughes RD, editors. *Acute liver failure: improved understanding and better therapy*. London: Mitre Press; 1991. p. 6–10.
- [2] Schiodt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999;5:29–34.
- [3] Ascher NL, Lake JR, Emond JC, et al. Liver transplantation for fulminant hepatic failure. *Arch Surg* 1993;128:677–82.
- [4] Blei AT, Olafsson S, Webster S, et al. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993;341:157–8.
- [5] O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439–45.
- [6] Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis* 1986;6:97–106.
- [7] O'Grady JG, Gimson AE, O'Brien CJ, et al. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988;94:1186–92.
- [8] Stange J, Ramlow W, Mitzner S, et al. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. *Artif Organs* 1993;17:809–13.
- [9] Weber C, Rajnoch C, Loth F, et al. The microspheres based detoxification system (MDS): a new extracorporeal blood purification procedure based on recirculated microspherical adsorbent particles. *Int J Artif Organs* 1994;17:595–602.
- [10] Rozga J, Podesta L, LePage E, et al. A bioartificial liver to treat severe acute liver failure. *Ann Surg* 1994;219:538–46.
- [11] Sussman NL, Gislason GT, Conlin CA, et al. The Hepatix extracorporeal liver assist device: initial clinical experience. *Artif Organs* 1994;18:390–6.
- [12] Fox IJ, Langnas AN, Fristoe LW, et al. Successful application of extracorporeal liver perfusion: a technology whose time has come. *Am J Gastroenterol* 1993;88:1876–81.
- [13] Chari RS, Collins BH, Magee JC, et al. Brief report: treatment of hepatic failure with ex vivo pig-liver perfusion followed by liver transplantation. *N Engl J Med* 1994;331:234–7.
- [14] Harland RC, Platt JL. Prospects for xenotransplantation of the liver. *J Hepatol* 1996;25: 248–58.
- [15] Coy D, Blei AT. Portal hypertension. In: Berk J, Schaffner F, editors. *Bockus textbook of gastroenterology*. Philadelphia: Saunders; 1994. p. 1955–87.

- [16] Velazquez RF, Rodriguez M, Navascues CA, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003;37(3):520–7.
- [17] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334(11):693–9.
- [18] Gores GJ, Nagorney DM, Rosen CB. Cholangiocarcinoma: is transplantation an option? For whom? *Hepatology* 2007;47(4):455–9.
- [19] Cordoba J, Blei AT. Treatment of hepatic encephalopathy. *Am J Gastroenterol* 1997;92:1429–39.
- [20] Chari RS, Gan TJ, Robertson KM, et al. Venovenous bypass in adult orthotopic liver transplantation: routine or selective use? *J Am Coll Surg* 1998;186:683–90.
- [21] Ferraz-Neto BH, Mirza DF, Gunson BK, et al. Bile duct splintage in liver transplantation: is it necessary? *Transpl Int* 1996;9(Suppl 1):S185–7.
- [22] Clavien PA, Harvey PR, Strasberg SM. Preservation and reperfusion injuries in liver allografts: an overview and synthesis of current studies. *Transplantation* 1992;53:957–78.
- [23] Reyes J, Gerber D, Mazariegos GV, et al. Split-liver transplantation: a comparison of ex vivo and in situ techniques. *J Pediatr Surg* 2000;35:283–9.
- [24] Ghobrial RM, Yersiz H, Farmer DG, et al. Predictors of survival after in vivo split liver transplantation: analysis of 110 consecutive patients. *Ann Surg* 2000;232:312–23.
- [25] Greig PD, Woolf GM, Sinclair SB, et al. Treatment of primary liver graft nonfunction with prostaglandin E₁. *Transplantation* 1989;48:447–53.
- [26] Abbasoglu O, Levy MF, Testa G, et al. Does intraoperative hepatic artery flow predict arterial complications after liver transplantation? *Transplantation* 1998;66:598–601.
- [27] Douzdjian V, Abecassis MM, Johlin FC. Sphincter of Oddi dysfunction following liver transplantation: screening by bed-side manometry and definitive manometric evaluation. *Dig Dis Sci* 1994;39:253–6.
- [28] Broelsch CE, Emond JC, Whittington PF, et al. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. *Ann Surg* 1990;212:368–75 [discussion: 375–7].
- [29] Wachs ME, Bak T, Karrer FM, et al. Adult living donor liver transplantation using a right hepatic lobe. *Transplantation* 1998;66:1313–6.
- [30] Abecassis M, Koffron A, Fryer J, et al. Surgical techniques in living liver donors. *Curr Opin Organ Transplantation* 2001;6.