29 Liver Transplantation for Hepatic Failure

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- *Patient and graft survival after liver transplantation (LT) has improved over time. Despite the options available to increase the donor pool, the expansion on indications for LT has surpassed the availability of grafts, exacerbating the scarcity of grafts.*
- *Clinical evaluation of potential recipients is crucial to avoid excessively early LT (with no benefit for patients with a good predicted survival without LT) but also excessively late LT (resulting in poorer outcomes). Timing and methods for organ allocation remain challenging.*
- *Partial liver grafts (including living-donor and splitted grafts) and marginal grafts represent options to increase the graft pool.*
- *Postoperative complications after LT remain significant and are mainly related to graft quality, recipient clinical status, immunosuppression, recurrence of hepatic disease, and technical aspects.*
- *LT in the setting of acute liver failure is uncommon and is accompanied by specific factors related to organ allocation and technical aspects.*

INTRODUCTION

The first human liver transplantation (LT) was performed in 1963 by Thomas Starzl.[1,2] The first liver transplantation with long-term survival (18 months) was performed in 1967.[3] During subsequent years, outcomes after orthotopic liver transplantation (OLT) remained poor, with a 1-year survival rate of 30%.[4] Progress in immunosuppressive therapy and surgical and anesthetic techniques, among other factors, led to improved long-term survival, and by the 1980s LT had become widely accepted as a definitive treatment for end-stage liver disease.[5] Currently, long-term survival prognosis after LT is excellent, with 1-year, 3-year, and 5-year survival rates of approximately 90%, 80%, and 75%, respectively.[6–8]

Liver transplantation became an optimal therapy for patients who have a short estimated life expectancy (less than one year) or a quality of life deemed unacceptable by the patient, due to a variety of liver diseases. Indeed, LT is currently the only definitive treatment for the management of the complications of cirrhosis and liver failure, and it is estimated that 6,000 to 7,000 LT procedures are performed each year worldwide.

The improvement in outcomes after LT has led to an increase in potential recipients. Consequently, the number of cadaveric donors in most countries has become insufficient. Alternatives to increase the donor pool (such as the use of split livers, non-heart-beating donors, and living donors) have alleviated organ scarcity, but globally the number of available organs is not adequate to eliminate the waiting list, and about 5-10% of patients die before receiving a graft.

In summary, indications for liver transplantation include decompensated cirrhosis, acute liver failure, certain malignancies (a subset of patients with hepatocellular carcinoma, cholangiocarcinoma, and metastatic endocrine tumors), and certain types of metabolic derangements. Liver transplantation for malignancies is discussed further in **Chapter 30** (*Liver transplantation for malignant and benign liver tumors*).

LIVER TRANSPLANTATION FOR END-STAGE LIVER DISEASE

INDICATIONS

The most common etiologies of chronic end-stage liver disease (ESLD) requiring OLT are cirrhosis from chronic viral hepatitis C or B, and from alcohol abuse. Other chronic liver diseases that may require OLT include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH), hemochromatosis, alpha-1-antitripsin deficiency, biliary atresia, autoimmune hepatitis, Wilson's disease, hepatic veno-occlusive disease, Budd-Chiari syndrome, and other vascular liver diseases.

Liver transplantation for ESLD is usually indicated when estimated survival is less than one year or quality of life has deteriorated significantly. Predictors of poor survival in cirrhosis include complications such as ascites, gastrointestinal bleeding due to portal hypertensive gastropathy or esophageal varices, synthetic dysfunction, hepatopulmonary syndrome, and portopulmonary hypertension, encephalopathy, and liver cancer.

Thus, specific criteria were determined to select adult patients with chronic liver disease for OLT, as follows:

- Liver cirrhosis classified as Child-Pugh A (**Table 1**), with at least one of the following complications: i) upper gastrointestinal bleeding secondary to portal hypertension, with two or more distinct episodes requiring blood transfusions; ii) hepatopulmonary syndrome with clinical manifestations; and iii) portosystemic encephalopathy.
- Liver cirrhosis classified as Child-Pugh B or C, regardless of complications.
- Primary biliary cirrhosis with a one-year survival prediction of less than 90% according to the mathematical models offered by King's College Hospital or the Mayo Clinic (**Table 2**).
- Primary sclerosing cholangitis, with at least one of the following conditions: i) presence of recurrent cholangitis with more than one episode; ii) prediction of 1-year survival of less than 90% according to the mathem atical models of King's College Hospital or the Mayo Clinic (**Tables 3 and 4**).
- Familial amyloid polyneuropathy (FAP) with disability score grades I, II and III (**Table 5**).

In addition to the Child-Pugh score, the MELD (Model for End-stage Liver Disease) score has been used to assess prognosis for cirrhosis from etiologies other than primary biliary cirrhosis and primary sclerosing cholangitis.

Table 1. Modified Child-Pugh score.

	1 point	2 points	3 points
Ascites	Absent	Controlled	Refractory
Total bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	< 2.8
INR	<1.7	1.7 – 2.2	> 2.2
Encephalopathy	Absent	Grade 1 or 2	Grade 3 or 4

Sum of parameters 1 to 6 = Child A; 7 to 9 = Child B; 10 to 15 = Child C.
INR: International normalized ratio.

Table 2. Mayo model for predicting prognosis in primary biliary cirrhosis.

R=0.051(age [y]) + 1.209 $\log_e$(bilirubin [mg/dL]) – 3.304 $\log_e$(albumin [g/dL]) + 2.754 $\log_e$ (PT [s]) + 0.675 $\log_e$(edema score)

Edema score: 0 for no edema without diuretics; 0.5 for edema without diuretics or edema resolved with diuretic therapy; 1 for edema despite diuretic therapy.

Table 3. Independent predictors of survival used in mathematical models for primary sclerosing cholangitis.

Mayo model	Revised Mayo model	King's College model
Age	Age	Age
Total bilirubin	Total bilirubin	Hepatomegaly
Histologic stage	Albumin	Histologic stage
Hemoglobin	AST	Splenomegaly
Inflammatory bowel disease	Variceal bleeding	Alkaline phosphatase

AST: aspartate aminotransferase.

Table 4. Mathematical models predictors of survival in primary sclerosing cholangitis.

Mayo model	R = 0.06 (age [y]) + 0.85 $\log_e$ (bilirubin [mg/dL]) - 4.39 $\log_e$ (hemoglobin in [g/dL]) + 0.51 (histological stage) + 1.59 (indicator for inflammatory bowel disease)
Revised Mayo model	R= 0.03 (age [y]) + 0.54 $\log_e$ (bilirubin [mg/dL]) + 0.54 $\log_e$ (aspartate aminotransferase [U/L]) + 1.24 (variceal bleeding [0/1]) – 0.84 (albumin [g/dL])
King's College model	R = 1.81 (hepatomegaly [0/1]) + 0.88 (splenomegaly [0/1]) + 2.66 $\log_e$ (alkaline phosphatase [mg/dL]) + 0.58 (histological stage) + 0.04 (age [y])

The MELD score (**Table 6**) is on a continuous scale from 6 to 40, with estimated three-month survival varying between 90% and 7%, respectively. This score has been used extensively by transplant centers to prioritize grafts to recipients with shorter survival expectancy.

CONTRAINDICATIONS

Contraindications to LT are mainly those conditions leading to poor early or late post-transplantation outcome. Relative contraindications are those correctable prior to transplantation and absolute contraindications are those that are not modifiable, precluding OLT.

Some accepted contraindications to LT are: i) very poor performance status precluding the patient from withstanding surgery; ii) uncontrolled extrahepatic sepsis; iii) alcohol abuse or illicit drug use with less than six months of abstinence; iv) anatomical conditions that rend graft implant technically impossible (such as extensive venous thrombosis); v) extrahepatic malignancy or hepatic malignancies with poor survival prognosis after LT (such as most liver metastases and cholangiocarcinoma, and advanced hepatocellular carcinoma); vi) lack of adequate social support; and vii) acquired immunodeficiency syndrome (AIDS).

Other unsuitable conditions include advanced age, hepatopulmonary syndrome, human immunodeficiency virus (HIV) infection, severe portopulmonary hypertension, and hemodynamic instability. It is important to note that HIV infection and replicative hepatitis B are no longer considered absolute contraindications for LT.

RECIPIENT EVALUATION

Candidates for LT should be investigated extensively in order to establish severity of hepatic disease and comorbidities. Surgical difficulties can be anticipated in recipients with prior abdominal surgery, obesity, and portal vein thrombosis.

Obesity seems to increase surgical risk and to reduce long-term survival following LT.[9–12] Despite a dearth of evidence of reduction in risk with preoperative weight loss, weight reduction should be attempted prior to surgery, and a body mass index of 40 kg/m^2 is a relative contraindication to LT.

Initial cardiac evaluation, including non-invasive stress echocardiography, is performed in all LT candidates to assess perioperative risk and to exclude concomitant cardiopulmonary disorders that preclude surgery or adequate long-term outcome.[13] Coronary artery disease is present in 3-28% of liver transplant candidates.[14,15] Severe coronary artery stenosis (more than 70%) is treated with revascularization before LT. Severe valvular and/or ventricular dysfunction should be improved by medical therapies.[16]

Table 5. Neurological classification of familial amyloid polyneuropathy.

Score degree of disability	
I	Presence of sensory disturbance in the legs and preserved ability to walk
II	Difficulty walking and strolling without orthoses
III A	Patient able to walk only with the aid of a crutch/cane
III B	Need two crutches / walking sticks
IV	Limited to wheelchair or bed

Table 6. Model for End-stage Liver Disease (MELD) score.

MELD = 3.78 ln(serum bilirubin [mg/dL]) + 11.2 ln(INR) + 9.57 ln(serum creatinine [mg/dL]) + 6.43 etiology (0: cholestatic or alcoholic, 1: otherwise)

If the patient has been dialyzed twice within the last seven days, use the value for creatinine as 4.0; any value less than 1 is given a value of 1.

Portopulmonary hypertension (mean pulmonary artery pressure of 25 mmHg or more in the presence of portal hypertension) is detected in 4-8% of LT candidates.[17] Mild and severe pulmonary hypertension (mean pulmonary artery pressure ≥ 25 mmHg and ≥ 50 mmHg, respectively) are associated with 50% and 100% mortality rates, respectively.[18] Vasodilator therapy should reduce the mean pulmonary artery pressure to less than 35 mmHg in order to minimize surgical risk.[19–21]

Hepatopulmonary syndrome (HPS) results from intrapulmonary vascular shunting and is present in 5-32% of LT candidates.[22] Liver transplantation reverses hepatopulmonary syndrome in most patients.[23] Thus, hepatopulmonary syndrome does not preclude LV, despite a high morbidity rate if severe HPS is present.[24–27]

Renal dysfunction in cirrhotic patients also has deleterious effects on early outcomes and should be actively evaluated to determine etiology and prognosis. The most common cause of renal dysfunction prior to LT is hepatorenal syndrome (HRS).[28] Simultaneous liver kidney transplantation may be indicated in selected cases of end-stage renal disease with cirrhosis or end-stage liver failure with chronic kidney disease.

Patients with liver dysfunction are more prone to have infectious diseases, such as spontaneous bacterial peritonitis and urinary and respiratory infection.[29]

These infections should be treated before LT. Additionally, serological tests for viral infections (hepatitis A, B, and C; Epstein-Barr virus; cytomegalovirus; herpes simplex; and HIV), syphilis, tuberculosis, and coccidiodomycosis are required. Treatment or prophylaxis is undertaken according

to results.

Hepatitis C. Cirrhosis due to chronic hepatitis C virus (HCV) infection is the most common indication for LT in most Western countries. Reinfection occurs in most patients after LT, since antiviral therapy is not curative, and 20-30% of patients develop cirrhosis. Liver failure due to recurrent HCV after liver transplantation occurs in 10% of patients within five to 10 years,[30,31] resulting in poorer outcomes than LT for other etiologies. If there is no contraindication to interferon and ribavirin (or other new protocols) therapy, HCV should be treated before LT, especially for more favorable HCV genotypes (II and III).[32]

Hepatitis B. Liver transplantation for cirrhosis due to hepatitis B virus (HBV) infection requires control of the virus prior to LT. Hepatitis B virus immune globulin (HBIG) in association with oral antiviral therapy results in adequate viral control before LT. Five-year graft survival in patients undergoing LT for HBV can reach 85% with this approach. Indeed, the advent of efficacious oral antiviral agents has even reduced the needed for LT due to liver failure associated with HBV infection.[33]

Alcoholic liver disease. Cirrhosis due to alcohol abuse is usually the second most common indication for LT. Alcohol dependence is responsible for a high rate of resumption of alcohol abuse after LT, leading to an incidence of graft failure of 2% by 10 years.[34] Patients should be in abstinence for at least six months prior to LT.

Primary biliary cirrhosis and primary sclerosing cholangitis. Indications for LT in primary biliary cirrhosis (PBC) are similar to those for other causes. Decompensated PBC is the main indication, but also uncontrollable severe pruritus may be an indication for LT. Primary sclerosing cholangitis (PSC) is associated with an increased risk of cholangiocarcinoma and gallbladder carcinoma. Liver transplantation is indicated for decompensated disease. Also, recurrent bacterial cholangitis and cholangiocarcinoma (in selected cases) represent indications for LT. Specific scores to predict survival in PBC and PSC are helpful to define the optimal timing for LT in these diseases (see above).

LISTING AND TIMING

Timing of LT plays a crucial role in outcomes. Excessively early transplantation may not benefit patients with a good predicted survival without liver transplantation, since one-year mortality after orthotopic liver transplantation can reach 10%. On the other hand, transplantation in the sickest and decompensated patients typically has the worst outcomes, and patients should meet minimal conditions to withstand surgery. Finding the ideal timing for transplantation and the most beneficial distribution of grafts available can be challenging. Usually, patients with ESLD are referred for LT when a decompensation occurs, e.g. ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatocellular carcinoma. The American Association for the Study of Liver Diseases (AASLD) guidelines suggest referring patients with a Child-Pugh score ≥7 and/or a MELD score ≥10.[35]

Scarcity of grafts has led to the prioritization of patients with poorer prognosis. Score systems, such as the MELD score, have been validated to predict short-term mortality in patients with ESLD. Besides serum bilirubin, serum creatinine, and INR, all used in the MELD score, other prognosis parameters have been suggested to be included in tools to prioritize liver grafts.[36,37] In addition, some exceptions should be considered, such as in cases of hepatocellular carcinoma, where prognosis is poor even with preserved liver function. Most centers add points to the MELD score in cirrhotic patients with hepatocellular carcinoma, to compensate for more preserved liver function. Other possible exceptions to MELD scoring include certain genetic disorders (primary hyperoxaluria, familial amyloidotic polyneuropathy, and some cases of cystic fibrosis) and other infrequent indications such as metastatic neuroendocrine tumors and hepatopulmonary syndrome.[38]

LIVER GRAFT DONORS

Most liver grafts are whole livers from deceased donors (brain death or, more recently, non-heart-beating donors). Donation after cardiac death is still controversial in some countries, since the results in this setting are poorer than when using brain death donors. Absolute contraindications for deceased organ donation are cancer and uncontrolled infections. However, grafts from donors with HCV can be used for HCV+ recipients, because recurrence and survival rates are similar to the use of HCV- donors. Also, grafts from donors with hepatitis B core antigen positive (anti-HBc+) have been used in association with recipient prophylaxis.[39] Age over 50 years, cardiac arrest or hypotension, high sodium, and liver steatosis have increasingly been accepted in order to increase the pool of donors. However, the use of marginal grafts may result in higher complication rates, such as primary graft non-function, early graft failure, biliary complications, and decreased graft survival. Grafts from donors over 70 years of age or that have more than 60% fat content should not be used, except as a bridge in urgent situations.[39]

Partial liver grafts from living donors or from splitted grafts are used in different proportions worldwide. Living-donor liver transplantation (LDLT) is a well-established method, largely used in Eastern countries. Some recent donor deaths have led to a decline in LDLT in Western countries.[40] Living-donor liver transplantation has the advantages of healthy donors, minimal ischemic time, and optimal timing of transplant. However, the surgery is more demanding than whole-organ transplantation and carries a risk for the donor.

Donor morbidity and mortality rates may reach 30% and 0.8%, respectively.[41,42] A recent meta-analysis including more than 5,000 patients compared surgical outcomes of LDLT and deceased donor LT, and found that biliary and vascular complications, in addition to need for re-transplantation, occurred more frequently after LDLT.[43] Identification of biliary variants and ensuring adequate venous outflow of the graft to the recipient are crucial.

Technical aspects of liver graft procurement for deceased living donors are detailed in **Chapter 32** (Technical aspects of liver transplantation) and summarized as follows. After assessment of macroscopic appearance of the liver and exclusion of contraindications to use it, a Cattel-Kocher maneuver allows for exposition of the retroperitoneum. The infra-renal aorta and portal vein are cannulated (usually by a tube inserted through the superior mesenteric vein). After clamping the thoracic aorta, infusion of cold preservation solution iinto the aorta and portal vein is started. The inferior vena cava is opened for discharge of blood. The liver is resected including the maximum vascular and biliary structures. The celiac trunk is usually resected along with a patch of the aorta. Attention should be paid to identify vascular variations, mainly those relating to arterial liver supply. After resection, the liver is packed in a sterile bag filled with cold conservation solution for transportation. During the back-table procedure, excess tissue attached to the liver and vessels is resected, eventual vascular reconstructions performed, and the graft is ready to be implanted (**Figure 1**).

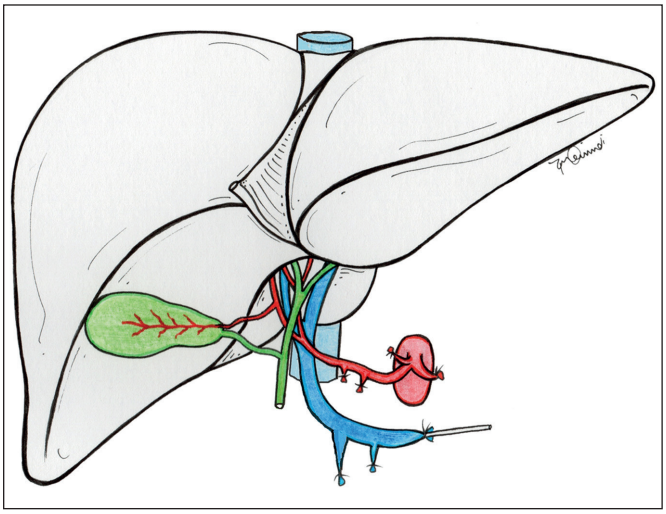

Figure 1. Whole liver graft after back-table preparation.

RECIPIENT SURGERY

Despite some technical variations, the surgical technique for whole liver transplantation has been standardized. Recipient portal hypertension can be a source of bleeding and careful hemostasis is mandatory from the time of incision to the end of procedure.[44]

During the first stage of the recipient operation, i.e. the native liver explantation, two methods are possible: with replacement or with preservation of the inferior vena cava (IVC). Replacement of the IVC requires IVC clamping, and a veno-venous bypass is usually used to prevent hemodynamic alterations and kidney hypoperfusion. The so-called piggyback method preserves the native IVC and only partial clamping is required for caval anastomosis. Results with these two methods are similar.

Technical aspects of recipient surgery can be summarized as follows. After section of all hepatic ligaments, the liver is completely mobilized. The hepatic hilum is dissected and the hepatic artery and bile duct sectioned close to the liver parenchyma. The portal vein is skeletonized along its entire length. A temporary end-to-side portocaval anastomosis may be used to prevent splanchnic congestion during the anhepatic phase, if the native IVC is preserved.[45] This technique reduces hemodynamic instability and could prevent the use of veno-venous bypass. The liver is then progressively dissected from the inferior vena cava and the hepatic veins sectioned to accomplish the native liver resection. Usually, the openings of the three hepatic veins are joined to obtain a sole large orifice. At this point, the suprahepatic IVC of the graft is anastomosed with the piggyback technique. The other vascular anastomoses are then performed. End-to-end portal anastomosis is performed followed by the arterial anastomosis. Less commonly, the arterial anastomosis is performed before the portal one. Finally, the biliary reconstruction is performed, generally with a choledoco-choledocal anastomosis. Additional details can be found in **Chapter 32** (Technical aspects of liver transplantation).

EARLY POSTOPERATIVE COMPLICATIONS

Despite advances in patient care, morbidity and mortality after liver transplantation remain significant. Several factors are implied in the occurrence of postoperative complications, including those related to graft quality, recipient clinical status, immunosuppression, and technical aspects. Most postoperative complications may be classified as: i) technical, ii) related to immunosuppression, iii) related to disease recurrence, and iv) graft dysfunction.

Most common technical complications are biliary (7-29% of cases), including biliary stenosis and/or fistula. Percutaneous treatment with biliary drainage and/or stenting is usually efficacious. In cases of early postoperative stenosis or refractory strictures, reoperation is indicated and choledoco-choledocal anastomosis recreated or a hepatico-jejunal anastomosis performed.[46] Arterial thrombosis is less common (2-10% of cases) and can lead to liver dysfunction, biliary fistula, cholangitis and sepsis. Treatment of hepatic artery thrombosis may be conservative or by reoperation

and arterial reconstruction. Technical complications in other vascular anastomoses are rare. Postoperative bleeding can lead to re-laparotomy in up to 5% of cases.

Infectious complications are the most common cause of death after LT.[47] Infection occurs in up to 80% of organ recipients; bacterial infections are most frequent (70%), followed by viral (20%) and fungal infections (8%). One quarter of deaths in LT recipients is due to infection. Immunosuppression should be individualized and prophylactic antibiotics used to prevent infections. Usually, high levels of immunosuppressive drugs in the early post-LT period are avoided, preventing renal dysfunction, systemic arterial hypertension, neuropsychiatric disturbances, and infections, especially those that are opportunistic. Graft function and patient recovery are initially evaluated by level of consciousness, urine output, and biochemical tests (such as lactate, transaminases, blood gas, blood count, urea, creatinine, bilirubin, gamma glutamil-transferase, prothrombin time and glucose levels).

Graft rejection occurs in approximately 20% of cases after LT. Acute cellular rejection is more common during the first four weeks after transplantation, but it can occur later. Clinical presentation is usually right upper quadrant pain, fever, malaise, and an increase in transaminases. Definitive diagnosis is established by percutaneous liver biopsy. In most cases, pulse administration of steroids and/or increasing immunosuppressant administration is effective. Chronic rejection is uncommon but usually requires re-transplantation. Primary graft non-function is an uncommon (1-7% of cases) but dramatic condition. It leads to multiple organ failure within a few days, and the treatment of choice is re-transplantation.

The length of intensive care unit (ICU) stay after LT has reduced noticeably from a mean of six days in the past to less than 24 hours in many centers nowadays.[48] Early extubation after liver transplantation has been successfully adopted in many centers and validated by a multicenter study.[49] However, preexisting comorbidities and intraoperative or postoperative complications can necessitate longer ICU stays.

LONG-TERM OUTCOMES

Long-term complications after liver transplantation are mostly related to side effects of immunosuppression, acute or chronic graft rejection, biliary complications, malignancies, and recurrence of the primary liver disease.[7,43,46,50–55]

Long-term immunosuppression (see details in **Chapter 31** – Immunosuppression) can be responsible for complications such as systemic arterial hypertension, new-onset diabetes mellitus, and dyslipidemia. New-onset diabetes mellitus occurs in one-quart of recipients after liver transplantation, mainly in the context of deceased donors.[56]

Renal failure is another common long-term complication, occurring in one quarter of recipients. Renal insufficiency is associated with decreased survival, and approximately 25% of patients will need kidney transplantation.[57]

Ischemic cholangiopathy represents a set of disorders characterized by multiple diffuse strictures affecting the graft biliary system in the absence of hepatic artery thrombosis or stenosis. Although its pathogenesis is unclear, it is associated with prolonged warm ischemic time. Biliary complications and ischemic cholangiopathy are more frequent (16-36%) with cardiac death (CD) donor grafts than with brain death (BD) donor grafts (3-17%), and most ischemic cholangiopathy occurs earlier after LT with CD donors (within 30 days) than with BD donors (within 90 days).[58] Treatment of biliary complications includes repeated therapeutic interventions and eventually re-transplantation.[59–62]

Recipients of liver transplant are more likely to develop malignancies. The most common cancers after liver transplantation include non-melanoma skin cancers, lymphoproliferative disease, colorectal cancer, lung cancer, oropharyngeal cancer, and Kaposi sarcoma.[63]

Almost all recipients with HCV infection will experience recurrence after LT, leading to a lower 7- to 10-year survival rate (60%) compared with those transplanted for other causes (75%).[64] Graft failure occurs in 5-8% of recipients during the first 12-18 months due to the development of fibrosing cholestatic HCV, and it is generally fatal.[65] Cirrhosis is found in 30% of recipients by five years after transplant. Antiviral treatment can result in virological clearance, but side effects of treatment can preclude its use.[66,67]

LIVER TRANSPLANTATION FOR ACUTE LIVER FAILURE

INDICATIONS, TIMING, AND RESULTS

Acute liver failure (ALF) is an uncommon (1-10 cases per million persons per year) but life-threatening critical clinical condition that occurs in patients who do not have preexisting liver disease.[68–72] It is characterized by a rapid deterioration of liver function, resulting in coagulopathy and encephalopathy within a few days or weeks after the onset of symptoms, and it is responsible for 4-7% of all liver transplantation.[73,74] Acute liver failure encompasses both fulminant hepatic failure (encephalopathy within eight weeks of the onset of symptoms) and subfulminant hepatic failure (or late-onset hepatic failure, up to 26 weeks after the onset of symptoms) and carries a high morbidity and mortality.

Acute liver failure is usually induced by toxins, drugs (e.g., acetaminophen [paracetamol]), or viral hepatitis (e.g., hepatitis A, B, C, D, or E). Less commonly, fulminant liver failure can be cryptogenic, related to ischemic hepatitis or

pregnancy-related diseases, or due to autoimmune hepatitis or Wilson's disease. The most common causes of ALF vary among countries. In the United States and Europe (particularly in United Kingdom), the most common cause of ALF is acetaminophen overdose (approximately 40-57% of cases), followed by idiosyncratic drug reactions; in Japan, the hepatitis B virus is the most common cause.[68,75,76]

Liver transplantation is the definitive treatment for liver failure, but a significant number of patients survive without transplant. Short-term transplant-free survival can be as high as 68% for patients with acetaminophen-related liver failure, or as low as 17% for patients with ALF from indeterminate cause.[77] It is crucial to rapidly and accurately identify those patients more likely to benefit from emergency LT. Clinical indicators are helpful to predict outcomes. Acute liver failure due to acetaminophen, hepatitis A, ischemic hepatitis, or pregnancy-related disease is less fatal without LT than acute liver failure from other etiologies (mortality 50% vs. 75%, respectively). The degree of hepatic encephalopathy is also predictor of survival without transplant. More severe (Grade III and IV) encephalopathy is associated with poorer spontaneous survival. However, many patients with ALF are not candidates for LT due to very poor clinical status or rapid clinical deterioration. In fact, 15-30% of patients with ALF die before liver transplant from cerebral death, infection, or multiple organ failure.[78,79]

Several prognostic scoring systems have been developed to predict spontaneous survival and then select patients for urgent LT, leading to a 1-year patient survival after orthotopic liver transplant of 60-70%.[80] The most widely applied criteria for LT in cases of ALF are King's College Hospital criteria (KCH criteria) and Clichy's criteria (**Tables 7** and **8**, respectively). These score systems have shown high positive and negative predictive values for mortality or LT.[81–85] However, relying entirely upon these scoring systems as a means of indication for LT is not recommended. It appears that survival in the context of ALF depends on a variety of factors, including etiology, grade of encephalopathy, ability of liver regeneration, and absence of other complications.

Table 8. Clichy criteria for liver transplantation on fulminant hepatic failure.

Presence of hepatic encephalopathy and factor V level:
<30% of normal in patients >30 years of age
<20% of normal in patients <30 years of age

One-year survival after LT for ALF is poorer than LT for chronic end-stage liver disease; however, following the first year, patients who have undergone transplant for ALF have a better long-term survival.[86–88] Most deaths after transplant for ALF occur within the first three months, and are usually due to neurological complications or infection.[68]

Selected patients with acute-on-chronic liver failure – a clinical entity defined recently – and severe alcoholic hepatitis may also represent potential extensions of transplant indication.[89]

TECHNICAL ASPECTS

Patients with ALF are more susceptible to hemodynamic instability during cava or portal clamping, since they usually do not have collateral circulation. Consequently, intracranial hypertension and inappropriate renal perfusion are more frequent than in patients with portosystemic shunts.[90,91] Extracorporeal bypass or the piggyback technique are methods to prevent hemodynamic instability due to clamping of the inferior vena cava. Temporary portocaval anastomosis during liver transplant with the piggyback technique is also useful to prevent hemodynamic changes due to portal clamping (**Figure 2**).[92–95]

Table 7. King's College criteria for liver transplantation on fulminant hepatic failure.

Acetaminophen-induced liver failure
- Arterial lactate >3.0 mmol/L after adequate fluid resuscitation - pH <7.3 - INR >6.5 AND creatinine >3.4 mg/dL in patients with grade 3 or 4 hepatic encephalopathy
Non-acetaminophen-induced liver failure

- INR ≥6.5 (prothrombin time >100 seconds)
- Three of the following:
  - Serum bilirubin ≥17.6 mg/dL (300 mmol/L)
  - non-A non-B hepatitis, idiosyncratic drug reaction
  - age <10 or >40 years
  - duration of jaundice before hepatic encephalopathy >7 days
  - INR >3.5 (prothrombin time >50 seconds)

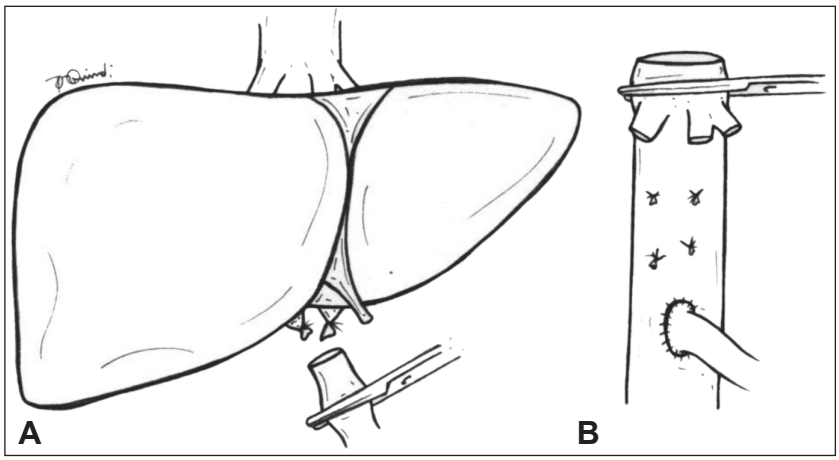

Figure 2. Schematic representation of temporary portacaval shunt during liver transplantation. **A**) Distal section of portal vein. **B**) End-to-side portacaval anastomosis and preservation of native inferior vena cava. This procedure reduces hemodynamic instability during the liver transplantation for acute liver failure.

Living liver donor and auxiliary liver transplantation

In addition to whole-organ LT from deceased donors, living donor liver transplantation (LDLT) has been attempted for ALF. Despite favorable survival following LDLT for ALF (approximately 75% 1-year survival), its use is controversial, mainly due to the need for compressed donor evaluation, which carries a risk of being incomplete, and risk of donor death (estimated at 0.2%).[42,96–98]

Another variant of liver transplant for ALF is auxiliary liver transplant, where the recipient's liver is kept in place and a partial graft (left or right) is implanted. The rationale for this technique is that a significant proportion (approximately 20%) of patients that fulfill criteria for LT are transplanted unnecessarily, because they would survive without liver replacement. Patients with severe ALF and a short interval between jaundice and encephalopathy are more likely to have liver regeneration.[99–101]

Auxiliary liver transplant provides a temporary substitute for metabolic and excretory functioning, allowing for reversion of brain edema and preventing brain damage. The criteria for auxiliary liver transplantation should be the same as that for orthotopic standard liver transplantation. Usually both the recipient and donor livers are size reduced in opposite sites (e.g. resection of the left lobe of a recipient liver and resection of the right lobe of a whole-organ graft) and the graft implanted in the orthotopic position (**Figure 3**). During donor liver reduction, the lobe not used for auxiliary transplant can be discarded or eventually used for another recipient as part of a split-liver transplantation.[102] Grafts from living donors can also be used in auxiliary liver transplantation. The hepatic resection on the recipient is usually facilitates by the liver atrophy in fulminant liver failure. Advantages of positioning a partial graft orthotopically include avoiding increased intra-abdominal pressure (since the graft plus remnant recipient liver result in a volume similar to that of a whole recipient liver) and allowing an adequate portal flow (with hepatotrophic factors) to the graft.[100,103] Conventional immunosuppression is continued until evidence of sufficient regeneration of the native liver appears (on the basis of histological, scintigraphical, and morphological data). After that, immunosuppression is progressively tapered, inducing chronic rejection with subsequent atrophy of the graft. Immunosuppression can be stopped abruptly, which is likely to be followed by severe and symptomatic rejection requiring surgical removal of the graft.[102,104]

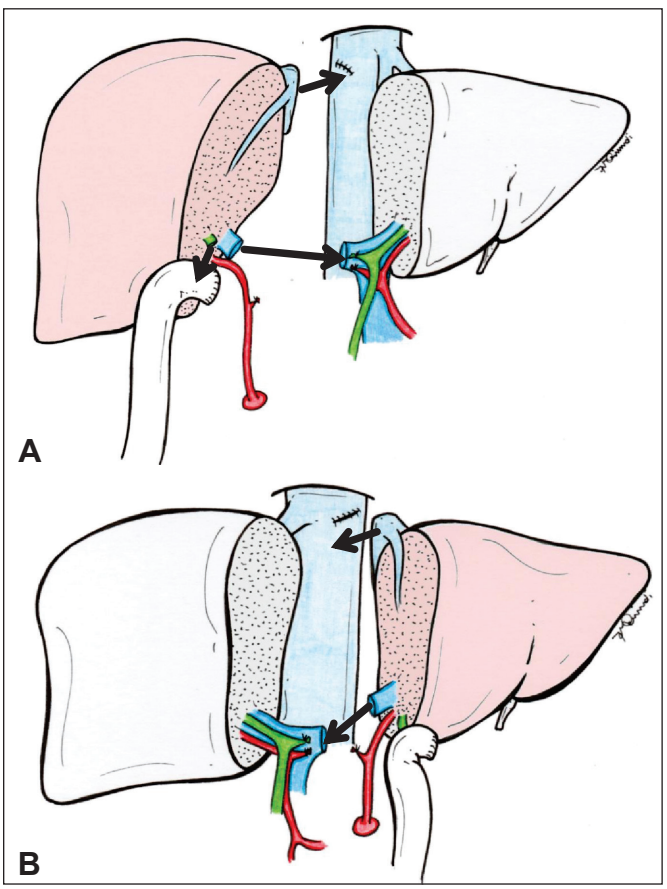

Figure 3. Auxiliary partial liver transplantation. **A**) Right graft implanted after right hepatectomy. **B**) Left graft implanted after left hepatectomy.

SUGGESTED READING

Agopian, V. G. *et al.* The evolution of liver transplantation during 3 decades: analysis of 5347 consecutive liver transplants at a single center. *Ann. Surg.* **258**, 409–421 (2013).

One of the largest series of liver transplantation showing an increase in patient and graft survival rates after implementation of the MELD (Model for end-stage liver disease). Several predictors of survival are identified.

Martin, P., DiMartini, A., Feng, S., Brown, R. & Fallon, M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* **59**, 1144–1165 (2014).

An extensive review of the literature and recommendations about evaluation and indication for liver transplantation.

Petrowsky, H. & Busuttil, R. W. Evolving surgical approaches in liver transplantation. *Semin. Liver Dis.* **29**, 121–133 (2009).

A description of evolving surgical approaches in liver transplantation discussing mainly methods using partial grafts (living donor and splitted grafts).

Bernal, W. & Wendon, J. Acute liver failure. *N. Engl. J. Med.* **369**, 2525–2534 (2013).

A well-structured review on acute liver failure, covering definition and causes as well as therapies and prognosis.

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