Medical Care of the Liver
Transplant Patient
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Preface

We are pleased to present the 4th edition of *Medical Care of the Liver Transplant Patient*. The idea to produce such a book started in 1994 at Duke University Medical Center, NC, USA, where a new program for adult and pediatric liver transplantation was developed. The goals were to produce valuable information for any physicians dealing with liver transplantation either in training, established in one field of transplantation or for general practitioners dealing with these patients. Dr Paul Killenberg was the main architect of this project with Dr P-A Clavien, and participated very actively up to the first 3 editions of the book. In 2009, Paul Killenberg died suddenly from a cardio-vascular event, and we would like here to underline his major contributions to the filed of hepatology and this book. Logically, the job of co-editor was taken by James Trotter, who was already involved with the book from his time at Duke University.

Since the 3rd edition published in 2006, there have been a number of novel developments in the field of liver transplantation including, the search to solve the problem of organ shortening with the use of extended criteria donors and particularly donors after cardiac death (DCD), new approaches and indications regarding liver transplantation for malignancies, and the treatment of a variety of infectious diseases. A number of new authors were invited to update previous chapters or write new chapters.

The 4th edition of the book has been extensively revised with many new chapters and was subdivided in four parts covering management of potential transplant recipient (Part 1), donor issue and management in the peri-operative period (Part 2), chronic problems in the transplant recipients (Part 3), and pediatric liver transplantation (Part 4). As new features, we have included learning points for each chapter, and questions to enable the readers to test their understanding of the key information. Sixteen new chapters were added, namely for Part 1: Management of renal disease; Management of hepato-pulmonary syndrome and portal-pulmonary hypertension; Cholestatic and autoimmune liver disease; Cholangiocarcinoma; Rare indications (rare tumors, Budd Chiari, etc); HIV patients; for Part 2: Extended criteria donor; Donation after cardiac death (NHBD); Transmission of malignancies and infection through donor organs; Domino and split transplantation; Coagulation and blood transfusion management; Acute care after liver transplantation; Rejection and immunosuppression; for Part 3: Prevention and treatment of recurrent viral hepatitis; PTLD and other malignancies after liver transplantation; Sexual function and fertility after liver transplantation.

We are grateful to our many colleagues who have agreed to author chapters in this book. We are also grateful to our colleagues at Wiley-Blackwell, Jennifer Seward, Rebecca Huxley, and Kathy Syplywczak, whose interest in this project has been so very important. We would like to also express our greatest gratitude to Madeleine Meyer, from the Zurich office, who played a major role in coordinating and making this edition possible.

P-A Clavien
James Trotter
January 2012
PART ONE

Management of the Potential Transplant Recipient
Selection and evaluation of the recipient (including retransplantation)

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\begin{mdframed}
\textbf{Key learning points}
\begin{itemize}
  \item Patients should be considered for liver transplantation if they have evidence of life-threatening complications of liver disease including cirrhosis and acute liver failure.
  \item Indications and contraindications perpetually change with regard to an organ shortage and medical improvements.
  \item Prioritization for transplantation is now determined by the Model of End Stage Liver Disease (MELD), which lists patients with the greatest risk of short-term mortality.
  \item At the liver center, a detailed evaluation of the recipient is performed to ensure that transplantation is indicated and feasible.
  \item Despite a high mortality comparing primary liver transplantation, retransplantation is the only therapy suitable for patients with loss of graft function.
\end{itemize}
\end{mdframed}

\section*{Introduction}

Selection and evaluation of a recipient for liver transplantation (LT) has become a great challenge, in the best interest of both the patient and society. Actually, limited organ availability and an increasing demand for organ transplantation has extended transplant waiting times and thus increased morbidity and mortality for potential recipients on waiting lists.

Patients should be referred to transplant centers when a life-threatening complication of liver disease occurs. A detailed medical evaluation is performed to ensure the feasibility of LT. Priority for transplantation has been determined by the MELD score, identifying patients with the highest estimated short-term mortality.

\textbf{Selection of the recipient: why liver transplantation should be performed}

Selection of the recipient is a main challenge for transplant physicians. LT is indicated in end-stage liver disease (ESLD). The most common indication in the adult is cirrhosis but the list of indications is growing. In contrast, the transplant community is currently faced with a major organ shortage; this has put extraordinary pressure on organ allocation programs. Since a successful outcome requires optimal patient
selection and timing, the issue of which patients to list for LT and when to transplant cirrhotic patients has generated great interest as well as considerable controversy.

Main indications for LT: complications of ESLD

LT should be considered in any patient with liver disease in whom the procedure would extend life expectancy beyond what the natural history of underlying liver disease would predict or in whom LT is likely to improve quality of life. Patients should be selected if expected survival in the absence of transplantation is 1 year or less, or if the patient has an unacceptable quality of life because of liver disease. Indications for LT in Europe are summarized in Figure 1.1.

Gastroesophageal variceal bleeding

Gastroesophageal varices are found in 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis. Variceal bleeding usually does not occur until the Hepatic Venous Pressure Gradient (HVPG) is above 12 mmHg. Each episode of bleeding carries a 20% mortality rate. If the varices are left untreated, after survival from the first episode, the rebleeding risk can be up to 70% within 1 year and is a major cause of death in patients with cirrhosis. Medical treatments are endoscopic variceal ligation and nonselective beta-blockers. Transjugular intrahepatic portosystemic shunt (TIPS) involves establishment of a direct pathway between the hepatic veins and the portal veins to decompress the portal venous hypertension that is the source of the patient’s hemorrhage. The procedure is technically challenging, especially in critically ill patients, and has a mortality rate of 30–50% in the emergency setting, but has <90% effectiveness in controlling bleeding from gastroesophageal varices. LT remains the best way to decompress the portal system if other therapy has failed.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric complication of cirrhosis in which clinical manifestations range from subtle personality changes and sleep disorder to coma. Although treatments have emerged, such as rifaximin to improve recurrence of HE, LT remains the only effective therapy.

Ascites and hepatorenal syndrome

Refractory ascites occurs in 5–10% of cirrhotic patients and carries a mortality rate of >50% at 2 years. Patients are prone to develop gastrointestinal variceal bleeding, hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) and HRS approximately 1 year after the development of ascites, reflecting the poor prognosis of patients with ascites. LT evaluation therefore should be instituted whenever refractory ascites develop.

Pulmonary complications

Hepatopulmonary syndrome (HPS) is found in 4–47% of patients with cirrhosis and is characterized by intrapulmonary vascular dilatations, especially in the basal parts of the lung. Liver injury and/or portal hypertension trigger the release of endothelin-1, TNF-alpha, cytokines and mediate vascular shear stress and release of nitric oxide and carbon monoxide, all
contributing to intrapulmonary vasodilatation. This results in hypoxemia which may require oxygen therapy. Because it could reverse HPS, LT is the only curative treatment. HPS differs from portopulmonary hypertension (PPHTN) which occurs in 2–8% of patients with cirrhosis. Imbalance between vasodilating and vasoconstrictive agents may be responsible for misguided angiogenesis and pulmonary hypertension. It is associated with a higher risk for LT and increased post-transplantation mortality.

Specific indications for LT

Some indications for LT are specific and vary depending on the underlying liver disease.

Cholestatic diseases

Some criteria for primary biliary cirrhosis (PBC) are specific (see Chapter 10). As survival rate is considerably reduced when the bilirubin level is over 100µmol/L for <1 year, this level is an indication of LT without any other complication. Uncontrolled and intolerable pruritus or major asthenia, even if isolated, are also indications for LT.

Primary sclerosing cholangitis (PSC) is a rare idiopathic cholestatic disease of unknown cause, characterized by a chronic fibrosing inflammation of the bile ducts (see Chapter 10). There is also an increased risk of cholangiocarcinoma, which is a difficult diagnosis with a prevalence over 30% after a 10-year disease course. Specific indications for PSC are longstanding severe jaundice (bilirubin level over 100µmol/L), cholestasis and pruritus not related to an acute episode of cholangitis, repeated episodes of cholangitis not controlled by antibiotics, and any suspicion of cholangiocarcinoma.

Autoimmune chronic hepatitis

Autoimmune chronic hepatitis is more common in young women. The clinical presentation of the disease is variable; classically it presents as active chronic hepatitis, but it may also present as established cirrhosis and in few cases as a fulminant course without chronic hepatic disease. A main characteristic of this disease is a good response to immunosuppressive treatment including steroids.

LT is indicated in autoimmune hepatitis for clinical decompensation, despite long-term adequate immunosuppressive treatment, or in fulminant hepatic failure, in which immunosuppressive treatment is usually ineffective and potentially deleterious.

Viral hepatitis

Chronic viral hepatitis due to the hepatitis virus B, C and/or D is one of the most common causes of ESLD worldwide and a frequent diagnosis in patients referred to transplant centers. Viral recurrence after LT is a major issue and graft damage secondary to viral re-infection may lead to graft failure, retransplantation or death.

Alcoholic liver disease

Alcoholic cirrhosis is a common liver disease and a significant number of patients with alcoholic liver disease receive LT. Several centers have developed an evaluation process based on medical and psychiatric criteria to better determine patients who would benefit most from the procedure. Abstinence from alcohol of at least 6 months is usually required to evaluate the need and timing of LT and to obtain better control of alcoholism. This interval is neither a consensus nor an absolute requirement. The risk of recidivism is estimated to be between 15–40% depending on the series, which seems to be related to the duration of follow up after LT and the duration of abstinence before transplantation. Whichever the case, this remains controversial.

Acute alcoholic hepatitis has been considered an absolute contraindication to liver transplantation on the grounds that patients with this disorder have been drinking recently and that a period of abstinence will allow many to recover. Unfortunately, many patients die during this interval. Patients who do not recover within the first 3 months of abstinence are unlikely to survive. Consequently, liver transplantation centers face a dilemma when caring for a patient with alcoholism who has severe alcoholic hepatitis and whose condition deteriorates despite adherence to abstinence, nutritional support, corticosteroids, and other elements of medical management.

Hepatobiliary malignancy

In certain cases, hepatobiliary malignancy is an indication for LT.

Hepatocellular carcinoma (HCC) is the commonest primary malignancy of the liver. LT is a suitable therapeutic option for early, unresectable HCC, particularly in the setting of chronic liver disease. The
study by Mazzaferro in 1996 established LT as a viable treatment for HCC. In this study, the “Milan criteria” were applied, achieving a 4-year survival rate similar to LT for benign disease. Since then various groups have attempted to expand these criteria (see Chapter 11).

Cholangiocarcinoma (CCA) is the second most common cancer among the primary hepatic neoplasm, accounting for 5–20% of liver malignancies. LT for CCA remains a controversial subject (see Chapter 12). A protocol combining neoadjuvant chemoradiation and LT was first used in patients with unresectable hilar CCA. Results have confirmed that this approach leads to significantly lower recurrence rates and higher long-term survival rates than other existing treatment modalities. Despite this, protocols to treat patients with CCA are not widespread, and are available at only a handful of transplant programs.

Other hepatobiliary malignancies may be successfully treated by LT, including without fibrolamellar carcinoma (without metastases), and hemangioendothelioma.

Classically, metastatic tumors of the liver have been considered a poor indication for LT, although some centers have performed this procedure associated with another therapy, such as chemotherapy and radiotherapy. In metastases from neuroendocrine tumors, liver transplantation could be indicated for patients with symptoms related to major hepatomegaly, hormone production, inavailability of effective therapeutic alternatives, diffuse metastases of the liver, slow-growing tumor and absence of extrahepatic disease. Transplant offers the main advantage of a significant improvement of the quality of life in many patients, an alternative to palliative therapy and a possible cure in some patients.

**Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis**

In the setting of the metabolic or insulin resistance syndrome (IRS), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are becoming increasingly common medical problems in the developed world. Patients with histological necrotic-inflammatory changes and/or fibrosis may progress to ESLD and require LT (see Chapter 9). It is likely that many potential LT candidates with NASH are excluded from LT due to co-morbid conditions related to IRS.

**Fulminant hepatitis**

Fulminant hepatitis is an emergency of LT. Viruses (especially hepatitis viruses A and B), drugs, and toxic agents are the most common causes of fulminant hepatitis; its prevalence varies between countries. The prognosis is essentially determined by neurological status, but is also affected very rapidly by damage to other organs. LT has revolutionized the prognosis of fulminant hepatitis, increasing the survival rate from 10–20% (all causes combined) to 75–80% at 1 year and 70% at 5 years (see Chapter 16).

**When to perform liver transplantation**

The timing of LT is crucial. Physicians have to determine which patients have liver disease that will endanger their lives before life-threatening systemic complications occur. This consideration is balanced by the risk of surgery and immunosuppressive treatment of LT if it is performed too early.

The timing of LT has changed in recent years, reflecting the modification in the method of organ allocation. Up until 2002, a patient’s position on the transplant list was determined by their time on the waiting list. The MELD score was implemented for determining organ allocation in 2002 in the USA. This score is an algorithm based on objective measures comprising creatinine, bilirubin and international normalized ratio (INR). The MELD was developed initially to determine the short-term prognosis for patients undergoing TIPS. It was considered to be highly accurate for predicting liver-related death. It was also regarded as a better system because it ignores waiting time and considers actual liver dysfunction.

Implementation of MELD led to an immediate reduction in liver transplant waiting list registrations for the first time in history of LT. Moreover, the median waiting time to LT decreased. In patients with MELD scores ≤14, the mortality rate with transplantation was found to be higher than that of patients with the same MELD score who had not undergone transplantation. Consequently, a MELD score higher than 15 is now considered a valid indication of LT in patients with ESLD. In contrast to the clear benefit of accurately estimating mortality for those patients on the waiting list, MELD has not been found to be as useful in predicting mortality following
LT. Mortality in the post-transplantation period is related not only to the degree of liver dysfunction prior to transplantation, but to other factors, such as donor characteristics, experience of the transplantation team, and random postoperative complications that cannot be predicted.

The MELD scoring system does have limitations. Not all candidates for LT suffer from diseases that carry an immediate mortality risk. These patients would not be well served by a priority system based solely on a mortality risk endpoint. Patients with HCC have relatively preserved synthetic function; they were not given priority in the early years of LT, which led to a high rate of death in these patients prior to LT. The MELD system offers a way to assign priority points for a diagnosis of HCC (see Chapter 11). Seventeen “exceptional diagnoses” have been identified to be underserved by the MELD score allocation system, including pulmonary complications of cirrhosis, hepatic encephalopathy, amyloidosis, and primary hyperoxaluria (Table 1.1). In these cases, extra points could be awarded to certain groups of patients as shown.

Even if the MELD scoring system is well-recognized to be a revolution in the LT era, some studies have tried to improve the model, incorporating values as serum sodium (MELD-Na), and age (integrated MELD). Another example is ΔMELD, using a time-dependent analysis. Some authors compared these models but the MELD score remains the only one used for organ allocation.

### Evaluating the recipient: Who shouldn’t be transplanted?

Evaluation of the recipient aims to identify contraindications of surgery as well as the contraindications to taking long-term immunosuppressive treatment. This assessment is not consensual and should be discussed in each transplant center. The contraindications to LT are dynamic, ever-changing and vary among liver transplant centers, regarding local expertise. There is an expectation that those transplanted would have a survival probability of at least 50% at 5 years with a quality of life acceptable to the patient. Figure 1.2 shows a sample decision tree for selection and evaluation of an LT recipient.

### Assessment of operability

The evaluation of the operability of the candidate requires a cardiovascular and respiratory assessment first.

To evaluate the cardiovascular risk, each patient should undergo an electrocardiogram and a trans-thoracic echocardiography to identify underlying heart disease. In patients with cirrhosis, increased cardiac output is described and the presence of latent cardiac dysfunction, which includes a combination of reduced cardiac contractility with systolic and diastolic dysfunction. Electrophysiological abnormalities are also noticed. This syndrome is termed “cirrhotic cardiomyopathy”. If the patient has multiple cardiovascular risk factors, a stress test should be carried out in order to reveal asymptomatic ischemic heart disease. A thallium stress test is now a minimally invasive and useful examination. In some cases, if coronary disease is suspected during the evaluation in high-risk patients, coronary angiography should be discussed.
vasodilators such as intravenous epoprostenol to decrease pulmonary vascular resistance. Careful perioperative attention is imperative to avoid right ventricular failure from acutely elevated pulmonary artery pressure or sudden increases in right ventricular preload. With increased surgical and anesthetic expertise, PPHTN is no longer considered an absolute contraindication for LT\(^2\)\(^3\) (see Chapter 5).

An evaluation of renal function is essential. HRS, usually a reversible cause of renal failure, has to be differentiated from other causes of chronic kidney disease that are potentially nonreversible and mandate simultaneous liver–kidney transplantations. Estimated renal clearance could be hard to determine in patients with cirrhosis.\(^2\)\(^6\) Performing inulin clearance and renal biopsies might help in the decision-making process. Chronic kidney disease patients with glomerular filtration rates of \(<30\) ml/min, HRS patients requiring renal replacement therapy for \(>8–12\) weeks, and patients with renal biopsy findings of \(>30\)\% fibrosis and glomerulosclerosis would benefit from receiving both liver and kidney grafts.\(^2\)\(^7\)

The general condition and nutritional status are sometimes difficult to assess in the patient with ESLD. Liver cirrhosis is associated with malnutrition. The clinical and biological parameters used may not apply in cases of severe hepatic insufficiency (body mass index, prealbumin etc.) More studies are needed to develop specific nutritional scores in cirrhosis.

Osteoporosis is also a common complication among patients with cirrhosis and may be detected by bone desitometry which can predict the risk of pathological fracture. An anesthesia consultation is mandatory at the end of this evaluation to assess operational risk. Human leukocyte antigen (HLA) typing and determination of blood group should be included in the general evaluation.

Anatomical evaluation
The surgeon must consider the type of vascularization of the recipient, mainly regarding the hepatic artery and portal system. The presence of shunts, which should be ligated during surgery, or the arcuate ligament are routinely sought. CT angiography of the liver is now performed in all recipients without contraindications. Hepatic arteriography has been largely replaced by CT angiography, but it is still indicated in cases of variant anatomy or previous hepatic surgery including LT.

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Figure 1.2 Proposed decision tree for selection and evaluation of LT recipient

To evaluate the respiratory risk, a lung function test and a chest X-ray are recommended to screen for lung disease related to cirrhosis or otherwise. When HPS or PPHTN are suspected, further investigation should be performed. The diagnosis of HPS is made by calculating the alveolar-arterial oxygen gradient and performing contrast echocardiography.

A diagnosis of PPHTN is made by performing echocardiography and right-heart catheterization when the systolic pulmonary artery pressure is higher than 30 mmHg on echocardiography.\(^2\)\(^4\) PPHTN used to be an absolute contraindication to LT. The pre-LT management of patients with PPHTN requires early diagnosis and chronic therapy with pulmonary
In the past, portal vein thrombosis (PVT) was considered an absolute contraindication for LT. Thanks to improvement in medical care, surgical techniques and radiological interventions, PVT by itself can represent an indication for LT. Several studies showed that surgical thrombectomy, thromboendovenectomy with venous reconstruction, interposition of vein graft, porto-caval hemitransposition and radiological endovascular interventions can resolve venous obstruction in liver transplant recipients. Interestingly, PVT patients’ rates of survival at 1 and 5 years after LT are equal.28

**Infection screening**

Patients with cirrhosis are prone to develop infections that could lead to the development of multiple organ failure and death.29 Screening for latent infections is required in order to treat a potentially lethal infections before LT and to prevent an exacerbation after LT under immunosuppressive regimens.

A chest radiograph should be performed to identify indirect signs of bacterial or fungal lung infection, including tuberculosis. Some teams recommend conducting a skin test. The search for the tubercle bacillus is not required in the absence of risk factors and with a normal chest radiograph for others.

Examination by an otolaryngologist, and a stomatologist could be required with a nasofibroscopy, a stomatological sinus radiography and panoramic radiographs. Latent dental infection should be treated if possible before LT.

Serologic evaluation for aspergillosis, syphilis, and legionella is often recommended. Hepatitis B and C are systematically sought, even if it is not the cause motivating the transplant. Human immunodeficiency virus (HIV) infection has been considered until recently as a contraindication for LT due to the poor spontaneous prognosis of HIV infection. The advent of highly active antiretroviral drugs (HAART) was a therapeutic breakthrough, and the prognosis has been dramatically improved. The progression of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) seems more rapid in co-infected patients, and a high number of patients will develop life-threatening liver cirrhosis. Patients with a controlled HIV disease are now considered suitable candidates for LT30 (see Chapter 14).

Serological tests of herpesviridae viruses (Epstein-Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, varicella zoster virus, human herpes virus 6 and 8) are conducted to determine the potential risk of reactivation after LT.

**Neoplasia screening**

Cancer screening must take into account age, gender, and alcoholic and smoking status of the recipient. If an extrahepatic cancer is an absolute contraindication for LT, a past history of cancer already treated should not disqualify candidates for LT, in accordance, case by case with an oncologist to estimate the survival and risk of recurrence at 1 year, 5 years, and 10 years under long-term immunosuppressive treatment. Actually, the LT should be performed if the risk of recurrence is estimated to be <10%. More often, physicians require a waiting period of 5 years to exclude potential recurrence. This fact should be balanced by the severity of hepatic illness. Colorectal cancer screening is mandatory for any candidate older than 50. If a colonoscopy under general anesthesia is too risky, CT colonography may be an alternative, although its usefulness in cirrhotic patients with ascites has never been demonstrated. The search for pulmonary neoplasia, stomatology, and of the ear–nose–throat (ENT), esophageal and bladder regions is mandatory in cases of alcohol and smoking addiction. An ENT examination is associated with a nasofibroscopy, and an examination of the oral cavity and an upper gastrointestinal endoscopy are recommended.

All women should have regular gynecological care including Papnicolaou test (Pap smear) and mammogram if needed. In men older than 50, screening for prostate disease should be done, including the quantification of PSA and a vesico-prostatic ultrasound.

An examination of the skin is important but skin cancer rarely contraindicates LT.

**Special screening for hepatic malignancy**

Preoperative baseline metastatic work-up includes a bone scan and chest computed tomography (CT). Recently, a positron emission tomography (PET) scan also tends to be included because of the usefulness to find undetected malignancy and to avoid legal issues.

**Social, psychiatric, and addiction assessment**

It is important to search for social network problems, psychiatric illness, and addiction in order to evaluate
the adherence of the recipient. In the case of hepatic encephalopathy, neuropsychological testing, CT brain scan, and electroencephalography could help to determine the reversibility of neuropsychiatric troubles. Drug or alcohol abuse is considered to be a contraindication to LT for many reasons: the risk of recidivism, risk of noncompliance, and risk of injury to the graft (see Chapter 6). A period of abstinence from alcohol for at least 6 months is generally a requirement though some teams currently criticize this rule. To date, other models should be defined to evaluate the risk of relapse, including a detailed psychiatric evaluation.

Stably abstinent, methadone-maintained opiate-dependent patients are generally good candidates for LT and show low relapse rates. Current toxicology screening methods provide a positive result of screening for cannabinoids up to 2 months after the patient’s last use. Patients who tested positive for marijuana had similar survival rates compared to those with negative test results. Whether patients who regularly use marijuana should be excluded from the waiting list remains a controversial issue.

Pre- and post-transplant smoking rates are high and cause significant morbidity and mortality by cardiovascular events or malignancies. Transplant teams should encourage smoking cessation treatments.

Age
The upper age limit for LT varies; the age of 65 is generally considered to be the upper limit but it has been successfully performed in patients as old as 70. The limit should be determined according to the patient’s general medical condition and discussed within each transplant center.

Evaluating and selecting a good recipient for LT requires the collaboration of several specialists. The final decision should be made within each center by expert multidisciplinary staff, considering the benefits and risks for each recipient.

Retransplantation
After LT, graft loss still occurs in 10–20% of adults. The most frequent causes of irreversible graft damage are primary nonfunction, hepatic artery thrombosis, graft rejection and recurrent diseases. Liver retransplantation (re-LT) is the only therapy suitable for patients with loss of graft function after a primary liver transplantation but re-LT carries a high morbidity and mortality rate compared with LT. The 1-, 5-, and 10-year patient survival rates after retransplantation were 61%, 53.7%, and 50.1%, respectively. These percentages were significantly less than those after LT during the same period: 82.3%, 72.1%, and 66.9%. In some centers patients could receive three, four, or more transplants.

Although re-LT is inferior to initial LT, it is the only means of prolonging survival in the patients whose initial graft has failed, making it an important contribution to overall survival.

Primary nonfunction
Primary nonfunction (PNF) is a postoperative condition characterized by absence of hepatic recovery due to various insults during harvesting, preservation or revascularization, unappreciated diseases in the donor, or accelerated rejection. Moderate steatosis of donor liver (30–60%) is associated with an increased incidence of PNF and re-LT rate. PNF, usually defined by the criteria of immediate graft failure with an elevated level of liver enzymes, scarce bile output, encephalopathy, and coagulopathy, is the main indication for re-LT. The incidence is around 6%. In the setting of PNF, re-LT should be undertaken early, within the first 7 days of the primary LT. As shown by multiple studies, re-LT at an intermediate time interval (8–30 d) is associated with a worse prognosis.

Hepatic artery thrombosis
Hepatic artery thrombosis (HAT) after LT can cause significant morbidity or mortality and lead to liver failure or septic complications. Allograft rejection is a possible cause of HAT. The incidence is near 3% (see Chapter 28).

Rejection
In the 1980s, acute hepatic allograft rejection occurred in approximately 80% of patients undergoing LT. Chronic rejection is always preceded by one or more episodes of acute rejection, and usually refractory to immunosuppressive therapy. Chronic rejection is an important cause of late graft failure. Despite improve-
The effect of allograft quality is exceedingly recognized as one of the important parameters that determine success of transplantation in general and re-LT in particular. More studies are needed to clearly define the parameters but older donors and a long, cold ischemia time (>8 hours) seem to be the key factors. HCV used to be considered as an independent risk factor for higher mortality rate, but several studies have demonstrated that a reasonable rate of survival can be achieved following re-LT and no significant survival differences are observed between HCV-positive, cryptogenic, cholestatic, or alcoholic liver disease patients when adjusted for age and MELD scores.38,39

These data suggest that the selection of the recipient should integrate the severity of illness, the interval time since the primary LT and the graft quality more than the cause of retransplantation.

Recurrence diseases

Hepatitis C
Approximately 20% or more of HCV-positive transplant recipients will develop allograft cirrhosis within 5 years after LT, and 10% of HCV-infected recipients will die or lose their allograft secondary to hepatitis C-associated allograft failure. The only solution is re-LT36 but for HCV-positive transplant recipients, re-LT remains highly controversial: patients undergoing re-LT for recurrent HCV have a significantly shorter median survival than those patients undergoing re-LT for other reasons of graft loss (see Chapter 32).

Hepatitis B
The use of hepatitis B immunoglobulin and nucleoside analogues has reduced the risk of HBV recurrence and led to the improvement of patient and graft survival rates.

Other liver diseases
Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis have a recurrence rate of 20–30% within 5 years after liver transplantation (see Chapter 33).

Timing for retransplantation
There is no consensus among transplant physicians to define specific re-LT survival outcomes below which re-LT is to be avoided. Only the MELD scoring system for organ allocation provides an objective stratification of retransplant candidates based on severity of illness.

A reduction in short-term survival rate to <60% was observed in all re-LT patients with a MELD score over 25. A7 While mortality was increased in all groups with a concomitant rise in MELD score, patients with a score over 30 had a survival rate of 20–40%. Retransplantation may exhibit survival rates similar to primary transplant in select patients. It is more likely to be successful in healthier recipients with a lower MELD score.

The references are as follows:

CHAPTER 1