Diagnosis and Management of Liver Disease

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Liver transplantation

DELAWIR KAHN and THOMAS STARZL

INTRODUCTION

Liver transplantation, the ultimate therapeutic option in liver disease, has ceased to be an experimental procedure. Indeed, transplantation, which is currently the treatment of choice for patients with chronic end-stage liver disease, should now be part of the therapeutic armamentarium of all practicing hepatologists.

The first human liver transplant was performed in Denver in 1963. The early years were difficult and the overall results poor, with only the minority of patients surviving for any significant period of time. However, it is noteworthy that nearly 20% of patients treated before 1979 are still alive 14 to 24 years later. The introduction of the new immunosuppressive drug cyclosporine in the late 1970s saw a dramatic improvement in the results of liver transplantation. This led to the important NIH Consensus Development Conference in 1983, where it was decided that liver transplantation should no longer be regarded as an experimental procedure but one that merited widespread clinical application. The late 1980s saw a phenomenal increase in the number of transplant centers and the number of patients being transplanted, not only in the USA and Europe but throughout the world. Indeed, over 2000 liver transplants were undertaken in the USA in 1989.

Several factors contributed to the dramatic improvement in the results of liver transplantation during the 1980s. The surgical procedure became standardized and can now be performed by any competent hepatobiliary surgeon. Refinements in the surgical technique include the introduction of the veno-venous bypass, the use of a 'growth factor' for the vascular anastomoses, standardization of the biliary anastomosis and modifications in the donor technique. Better patient selection, the introduction of new immunosuppression regimens, and improvements in organ preservation have also contributed to the improved results.

Many centers are now able to achieve 1-year survival figures in excess of 90% providing only good risk patients are treated. Patients who survive the first year after the transplant may expect a favorable long-term outcome with a low rate of attrition.

INDICATIONS FOR LIVER TRANSPLANTATION

The indications for orthotopic liver transplantation include chronic advanced liver disease, hepatic malignancy, fulminant hepatic failure and metabolic liver disease (Table 27.1).

Table 27.1 Indications for orthotopic liver transplantation

Chronic liver disease
Cholestatic liver disease
• primary biliary cirrhosis
• primary sclerosing cholangitis
• biliary atresia
Hepatocellular liver disease
• viral hepatitis
• alcoholic liver disease
• drug-induced liver disease
• autoimmune liver disease
• cryptogenic cirrhosis
Vascular disease
• Budd–Chiari syndrome
Hepatic malignancy
Hepatocellular carcinoma
Cholangiocarcinoma
Carcinoid
Fulminant hepatic failure
Viral hepatitis
Drug-induced
Metabolic liver disease
Wilson's disease
Tyrosinemia
Alpha-1 antitrypsin deficiency

The chronic liver diseases can be divided into those which are predominantly cholestatic in nature and include primary biliary cirrhosis, primary sclerosing cholangitis and biliary atresia, and those diseases which predominantly affect the hepatocytes and include chronic viral liver disease, chronic drug-induced liver disease, alcoholic liver disease and autoimmune liver disease. Some patients with the Budd–Chiari syndrome may also benefit from a liver transplant. Liver transplantation for hepatic malignancy is a controversial area since many of these patients die from recurrence of the tumor soon after the transplant. On the other hand, patients with chronic liver disease with an incidental small hepatoma noted in the resected liver do well after liver transplantation and have much the same prognosis as patients who are transplanted for end-stage liver disease. Some tumors appear to behave less aggressively. Indeed, patients with fibrolamellar tumors and hemangioendotheliomas do relatively well after transplantation. In addition, better survival and lower rates of recurrence have been reported after liver transplantation in patients with cirrhosis of the liver and a small (<5 cm) histologically non-invasive hepatocellular carcinoma when compared with liver resection. In contrast, cholangiocarcinoma is regarded as a relative contraindication to liver transplantation because of the high rate of recurrence and poor survival figures.

Liver transplantation for fulminant hepatic failure is another controversial area. Because of the unpredictable natural history of the disease, many patients with fulminant hepatic failure die before a suitable donor becomes available. Although a small number of patients in stage 4 coma may recover with medical support only, over 80% are likely to die as a result of their disease (Chapter 12). Thus transplantation should be considered in these patients.

Of great interest to some physicians are the various inborn errors of metabolism that are now potentially treatable by liver transplantation. These patients can be divided into those where the liver is severely damaged by cirrhosis, such as in cases of Wilson's disease, alpha-1 antitrypsin deficiency and tyrosinosis, and the liver transplant is indicated because of chronic liver disease, and those patients where the liver is morphologically normal although it contains a metabolic defect which is damaging

another system. For example, patients with familial hypercholesterolemia have normal lipid levels after liver transplantation.

CONTRAINDICATIONS TO LIVER TRANSPLANTATION

The contraindications to liver transplantation (Table 27.2) are being continually revised. Certain diseases in which transplantation might have previously been precluded or strongly discouraged are no longer absolute contraindications for transplantation.

Table 27.2 Contraindications to liver transplantation

Absolute contraindications
Sepsis outside the biliary tree
Advanced cardiopulmonary disease
Metastatic hepatic malignancy
AIDS
Relative contraindications
Portal vein thrombosis
Age >60 years
Advanced dialysis-dependent renal disease
HBsAg positivity
HIV-positive
Previous upper abdominal surgery
Cholangiocarcinoma
Hypoxemia with right to left shunts

Patients who have active sepsis outside of the liver and patients who have severe cardiac or respiratory disease are not considered as transplant candidates. Metastatic malignancy and AIDS are also regarded as absolute contraindications. A few centers have transplanted patients who are HIV-positive but without clinical AIDS. Various techniques have been devised to circumvent the problem of portal vein thrombosis and this is no longer a contraindication. Neither is age. Indeed, many patients over the age of 60 years have undergone successful orthotopic liver transplantation. Patients with advanced chronic renal disease can be subjected to kidney transplantation in addition to the liver transplant. Liver transplantation in patients who are hepatitis B surface antigen-positive remains controversial because of the high rate of recurrent disease after transplantation. However, many patients do survive long-term. Those patients who are HBV-DNA negative and those who receive immunoprophylaxis after liver transplantation have a more favorable prognosis. Upper abdominal surgery, in the form of portacaval shunts or major hepatobiliary surgery, add to the complexity of the transplant procedure. Cholangiocarcinoma is a relative contraindication because of the high incidence of recurrence of the tumor. Hypoxemia with right to left shunts is also regarded as a relative contraindication.

TIMING OF LIVER TRANSPLANTATION

One of the most difficult aspects of liver transplantation is the optimal timing of the transplant procedure. Many patients with chronic advanced liver disease die while awaiting liver transplantation. Furthermore, if one waits too long before referring patients for liver transplantation their general condition may deteriorate to a point where the outcome of the transplant procedure may be compromised. Thus early referral has to be balanced against operative mortality as well as long-term benefit. Guidelines have been devised to help in determining the best time for referring patients for transplantation (Table 27.3). Any patient with chronic advanced liver disease who has a major complication such as a major variceal bleed, intractable ascites, recurrent bacterial peritonitis or the development of the hepatorenal syndrome should be given the option of a liver transplant.

OPERATIVE PROCEDURE

In orthotopic liver transplantation, the

Table 27.3 Indications for liver transplantation

Acute liver failure
- Bilirubin >20 mg/l (400 µmol/l)
- Prothrombin time > 30 sec above control
- Progressive encephalopathy ≥ grade 3

Chronic liver disease

Cholestatic liver disease:
- Bilirubin > 12 mg/l (200 µmol/l)
- Intractable pruritus
- Advanced bone disease

Hepatocellular liver disease:
- Albumin < 2.5 g/l
- Hepatic encephalopathy worst grade ≥ 3
- Prolonged prothrombin time

Factors common to both
- Hepatorenal syndrome
- Recurrent bacterial peritonitis
- Refractory ascites
- Recurrent biliary sepsis
- Development of hepatoma
- Major variceal bleeding

diseased native organ is removed and replaced with a new liver in the most anatomically normal way possible. The technical aspects of the transplant procedure have undergone major refinements over the years, and have been described in detail elsewhere. Various techniques have been devised to circumvent anomalies of donor or recipient blood vessels. The introduction of the extracorporeal venovenous bypass in 1983 to decompress the splanchnic and systemic venous circulations during the anhepatic phase has been one of the most important refinements in the surgical technique. The venovenous bypass is used either routinely or selectively in patients with severe portal hypertension and compromised renal function or in those who fail a trial of cross-clamping. Reconstruction of the biliary tract has also become standardized and can be done either by connecting the donor and recipient common ducts end-to-end over a T-tube or the common duct of the donor to a jejunal limb in a Roux anastomosis.

IMMUNOSUPPRESSION

The introduction of the new immunosuppressant agent cyclosporine in the late 1970s led to a significant improvement in the results of solid organ transplantation. The search for new and more potent immunosuppressive drugs continues. Currently most patients receive a combination of cyclosporine, steroids and azathioprine after liver transplantation. Some centers have used a sequential immunosuppression regimen where a monoclonal or a polyclonal antibody is used for the first 7–10 days and cyclosporine introduced thereafter. This is done to minimize the nephrotoxic effects of cyclosporine. The new immunosuppressant agent FK506 was discovered in 1984 in the northern regions of Japan and has been shown, *in vitro*, to be many times more potent than cyclosporine. These initial findings were confirmed, *in vivo*, in heart, liver and kidney transplants in dogs, rats and primates. FK506 has been shown to be effective as a form of salvage or rescue therapy in patients who continue to reject the liver grafts despite conventional treatment of acute rejection. The initial multicenter trials comparing FK506 against cyclosporine showed better patient and graft survival in Europe but no difference in the USA compilations. However, in both series there was a different spectrum of side effects, less steroid-resistant rejection and lower steroid usage with FK506. Other immunosuppressive agents under investigation include brequinar sodium, dyspergaulin and RS61443.

LIVER PRESERVATION

The major advance in liver transplantation in the 1980s was the introduction of a new preservation medium, the Wisconsin solution. Although livers can be stored for longer than 24 hours, recent studies have indicated that ischemic times of longer than 12–15 hours are associated with a greater incidence

of primary non-function as well as delayed intrahepatic biliary strictures. However, liver transplants can now be performed as an elective procedure. It has also made it possible to increase the size of the donor pool and therefore increase the number of liver transplants being performed.

REDUCED-SIZE LIVER TRANSPLANTATION

The lack of organ donors continues to be a major limiting factor in transplantation. This is especially true for pediatric patients awaiting liver transplantation. To overcome this critical shortage of suitable-sized pediatric donors, a lobe or segments of an adult liver can be transplanted into a pediatric recipient. Mortality rates for children awaiting liver transplantation are now almost negligible. The results of reduced-size liver transplantation are as good as intact livers. In contrast, the results of split liver transplantation are poorer.

LIVING RELATED LIVER TRANSPLANTATION

The number of live related liver transplants and the number of centers performing this procedure have increased significantly in recent years. Graft and patient survival have been as good as intact liver transplantation. The risk to the donor has been acceptable with only one mortality documented thus far. The major advantage is that the transplant can be undertaken electively with the patient in optimal condition.

RECOMMENDED READING

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