Liver Transplantation

a report by
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Before transplantation, patients with end-stage liver disease (ESLD) in the form of ascites, hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding and/or hepatocellular carcinoma were likely to die within months to years, and therapy was mainly symptomatic and palliative. Liver transplantation has changed the outcome of these patients and, indeed, has become the most effective therapy in these circumstances. Survival rates now approach 90–95% and 65–80% after one and five years of follow-up, respectively.[1]

The number of patients undergoing liver transplantation has been constantly increasing, reaching a plateau limited primarily by the shortage of organs (see *Figure 1*). While in recent years the introduction of live donor liver transplantation and the increasing use of grafts from older and hepatitis C virus (HCV)-positive grafts has helped in maintaining this plateau, the organ demand will continue to out-strip the supply until adequate xenografts or hepatic stem cells can be used.

Indications and Contraindications

The indications for liver transplantation are numerous (see *Table 1*) but basically refer to acute or chronic liver failure from any aetiology. The most frequent indications in adults are chronic hepatitis C and, to a lesser extent, alcoholic liver disease, chronic hepatitis B, primary biliary cirrhosis, primary sclerosing cholangitis and auto-immune hepatitis.[2] Non-alcoholic fatty liver disease probably represents an increasing percentage of cirrhosis of unknown aetiology.

Patients with cirrhosis who develop complications (i.e. ascites, variceal bleeding or hepatic encephalopathy) and/or signs of hepatic insufficiency must be referred to an appropriate centre for a transplant evaluation.

Contraindications for liver transplantation have evolved with time (see *Table 2*). There remain few ‘absolute’ contraindications that eliminate a candidate from transplantation consideration; even these require careful individual consideration prior to denying a patient this opportunity. There are also very few ‘relative’ contraindications. In general, relative contraindications *per se* do not diminish the post-transplantation outcome, although the addition of several of them might impair survival and become an absolute contraindication.

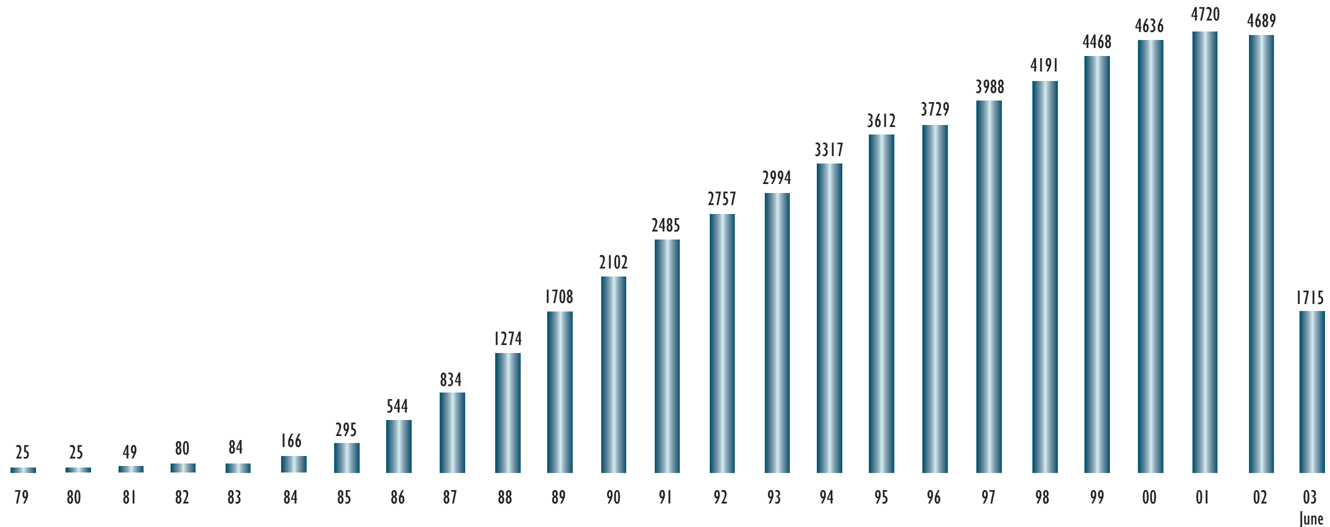
Listing Criteria

There are minimum criteria an adult should meet to be placed on the waiting list for liver transplantation. For the ESLD, the Child-Turcotte-Pugh scale (see *Table 3*) has been the preferred classification for listing patients. A score of at least seven is the minimum disease severity to include a patient in the waiting list, based on an anticipated one-year survival rate of less then 90%. For conditions in which survival is not correctly reflected by the score, such as hepatocellular carcinoma (HCC) or cholestatic liver diseases, other scores have been developed. For patients with HCC, the criteria usually used includes solitary tumours less than 5cm in diameter, or a maximum of three tumours with the largest measuring less than 3cm without metastases or vascular invasion. For cholestatic liver diseases, the Mayo risk score predicts survival more reliably than the Child-Turcotte-Pugh score.

In addition, the timing of liver transplantation involves determining when an individual will derive the maximum benefit from receiving a liver. The Model for End-Stage Liver Disease (MELD) score was recently created as an objective index to classify candidates for liver transplantation, based on the risk of dying on the waiting list.[3] This model

1. *Cardenas A, Gines P, “Management of complications of cirrhosis in patients awaiting liver transplantation”,* J Hepatol *(2005);42: S124–S133.*
2. *Carithers R L Jr, “Liver transplantation. American Association for the Study of Liver Diseases”,* Liver Transpl *(January 2000);6(1): pp. 122–135.*
3. *Malinchoc M, Kamath P S, Gordon F D, Peine C J, Rank J, TerBorg P L, “A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts”,* Hepatology *(2000);31: pp. 864–871.*

Figure 1: Evolution of Liver Transplantation in Europe



Data based on the European Liver Transplant Registry (ELTR).

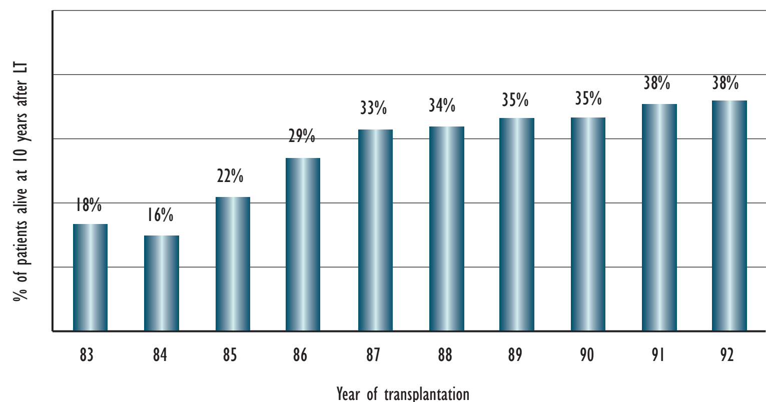
was initially created to allocate organs in most urgent need of transplantation and to minimize the impact of waiting time. The scoring system varies from six to 40 and is based on variables such as bilirubin, international normalised ratio and creatinine. In several studies, MELD has shown to better predict the risk of death than the Child-Pugh score and is therefore now used in many centres to prioritise transplantation.[4]

Management of Patients on the Waiting List

Interventions in pre-transplant patients are targeted at the reduction of life-threatening complications and assurance of a good post-transplant outcome. These measures include the appropriate management of the main complications of the advanced cirrhosis, i.e. the use of β-blockers or banding for the primary or secondary prophylaxis of variceal bleeding, endoscopic and medical treatment for active variceal bleeding and the use of lactulose/lactitol for preventing or treating hepatic encephalopathy. Ascites must be managed with diuretics and, if non-responsive, with therapeutic paracentesis including albumin reposition. Prophylactic antibiotherapy for spontaneous bacterial peritonitis should be used whenever indicated and vasoconstrictors should be used with albumin in cases of hepatorenal syndrome.

The medical assessment of patients on the waiting list should include screening for colorectal, prostate, breast and cervical cancer. Smoking cessation is of key importance and alcohol abstinence is mandatory. In addition, patients should receive vaccines against hepatitis A and B whenever indicated. Hepatocellular carcinoma should be screened with α-fetoprotein and imaging and should be managed aggressively.[5]

Figure 2: Evolution of the Rate of Patients who are Alive with their First Graft at Least 10 Years after Liver Transplantation



ELTR data, December 2003.

It is important to constantly re-evaluate patients on the waiting list to determine their continued appropriateness for liver transplantation.

Outcome

4. *Durand F, Valla D, "Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD",* J Hepatol *(2005);42: S100–S107.*
5. *Murray K F, Carithers R L Jr, "AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation",* Hepatology *(2005);41(6): pp. 1–26.*
6. *Belle S H, Porayko M K, Hoofnagle J H, Lake J R, Zetterman R K, "Changes in quality of life after liver transplantation among adults. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database (LTD)",* Liver Transpl Surg *(March 1997);3(2): pp. 93–104.*

Table 1: Indications for Liver Transplantation

Hepatocellular Cirrhosis
Viral (HCV, HBV)
Alcoholic
Autoimmune
Cryptogenic
Cholestatic Disorders
Primary biliary cirrhosis (PBC)
Primary sclerosing cholangitis (PSC)
Secondary biliary cirrhosis
Biliary atresia
Hepatic Malignancies
Hepatocellular carcinoma
Metastases from neuroendocrine tumours
Fulminant Hepatic Failure
Inherited, metabolic and vascular diseases
Hereditary haemochromatosis
Wilson disease
Alpha-1-antitrypsin deficiency
Non-alcoholic steatohepatitis (NASH)
Familial amyloid polyneuropathy
Type-1-glycogen storage disease (GSD)
Tyrosinemia
Polycystic disease
Budd-Chiari syndrome (BCS)
Veno-occlusive disease
Re-liver transplantation

Over the past three decades, notable advances and progression have been achieved in several transplant-related areas including pre-transplantation patient management, surgical techniques, perioperative care, immunosuppressive regimes and management of post-transplant complications. These improvements have led to increased survival rates following transplantation. Currently, survival rates typically reach 84% at one year (ELTR data, December 2003). In addition, long-term survival for adults approaches 75% at five years and 60% at 10 years. In Europe, 38% of the patients transplanted in 1992 were still alive with their first graft at least 10 years after the surgery, while the proportion was only 16% 20 years ago (see *Figure 2*).

An excellent quality of life is generally achieved after the procedure.[6–8] Patients return to gainful activities, and an increasing number of women have carried pregnancies to term.[9]

Future areas of study that may impact outcomes are the development of new immunosuppression protocols, treatment of recurrent hepatitis C, expansion of living donor transplantation and methods to support hepatocyte recovery in injured grafts.

Immunosuppression

Patients undergoing organ transplantation must receive immunosuppressive agents to prevent graft rejection. Substantial improvements have been made in this area and rejection currently does not pose a significant threat to liver transplant patients. Unfortunately, these agents are associated with significant side effects (i.e. hirsutism, gingivitis, diarrhoea and osteoporosis), immunodeficiency toxicity (e.g. infections and malignancies) and non-immune toxicity (e.g. nephrotoxicity, hypertension, diabetes, hyperlipidemia or neurotoxicity), which should be balanced against the risk of rejection on an individual basis. Indeed, the development of new agents, such as mycophenolate and sirolimus, with different side-effect profiles compared with the standard calcineurin inhibitors, has greatly helped in individualising immunosuppression.

Complications

Complications after transplantation can be divided into early post-operative complications and late complications. While management and outcome of early complications have improved in recent years, late complications, particularly the recurrence of the original liver disease and the development of *de novo* neoplasms, pose a threat to long-term survival.

Early Post-operative Complications

Graft-related complications include primary graft dysfunction (PGD) (2–20%), vascular complications (2–17%), biliary complications (10–35%) and acute cellular rejection (10–50%). With current immunosuppressive agents, the risk of rejection has decreased significantly and, if present, is generally responsive to therapy. In contrast, extrahepatic complications, particularly infections (75%), still pose a substantial risk in the early post-transplant course. Indeed, infections are responsible for most early deaths. Malnourished

7. *Bravata D M, Olkin I, Barnato A E, Keeffe E B, Owens D K, "Health-related quality of life after liver transplantation: a meta-analysis",* Liver Transpl Surg *(July 1999);5(4): pp. 318–331.*

8. *Burra P, De Bona M, Canova D, Feltrin A, Ponton A, Ermani M, Brolese A, Rupolo G, Naccarato R, "Longitudinal prospective study on quality of life and psychological distress before and one year after liver transplantation",* Acta Gastroenterol Belg *(January–March 2005);68(1): pp. 19–25.*

9. *Riely C A, "Contraception and pregnancy after liver transplantation",* Liver Transpl *(November 2001);7(11 suppl. 1): S74–76.*

10. *Haagsma E B, Hagens V E, Schaapveld M et al., "Increased cancer risk after liver transplantation: a population-based study",* J Hepatol *(January 2001);34(1): pp. 84–91.*

patients and patients requiring an intensive care unit (ICU) setting while awaiting transplantation are those at highest risk of severe infections. Invasive fungal infections in such patients have an extremely high mortality. In addition, both renal failure (50%) and neurological complications (35–50%) are serious morbidities that may impair long-term quality of life and potentially survival.

Late Complications

These include recurrence of primary disease, such as HCC, HBV and HCV-related cirrhosis, autoimmune-type diseases (discussed later in this article) and *de novo* malignancies. *De novo* neoplasms are the second cause of mortality in the long-term. The risk of *de novo* malignancies increases with time, reaching 55% at 15 years post-transplantation.[10] The most frequent are skin tumours, Kaposi sarcoma and post-transplant lymphoproliferative disease.
Other long-term complications include hypertension, osteopoenia, hyperlipidemia, diabetes mellitus and obesity. Chronic rejection rarely occurs. If diagnosed at an early stage response to potent immunosuppressive agents, including tacrolimus, mycophenolate and sirolimus, may occur.

Specific Indications for Liver Transplantation

HBV-related liver disease represents 5–10% of indications in most series. Due to recent improvements in the management of HBV infection, post-transplantation outcomes are now excellent, similar to those achieved by patients with cholestatic liver diseases. Historically, these patients had progressed poorly with transplantation. The five-year survival rate was reported to be 50% compared with 70–85% for patients with alcoholic or cholestatic liver diseases. This reduced survival was, in large part, related to the high rate of HBV recurrence in the absence of specific prophylactic therapies. In recent years, several new therapies, including hepatitis B immune globulin (HBIg) and oral antivirals, such as lamivudine and adefovir, have become available so that recurrence is effectively prevented (with a likelihood of recurrence down to 5–10% with HBIg plus lamivudine) and strategies can be tailored individually, based on risk of recurrence. Currently, the two major questions to be debated relate to the best long-term prophylactic strategy, and the optimal regimen and timing of pre-transplantation antiviral therapy.[11,12]

HCV-associated ESLD with/without HCC has become the leading diagnosis in patients undergoing liver transplantation. As with HBV, viral recurrence defined by the presence of HCV RNA in serum following transplantation occurs universally. Recurrence of infection is associated with histological evidence of liver injury in the majority of patients. Progression to cirrhosis occurs in a percentage that varies between 6% and 23% at a median of 3–4 years post-transplantation, with cumulative risks at 5–7 years, ranging from 10–44%. Unfortunately, liver enzymes do not correlate with either viremia of histological findings, hence providing the justification for protocol liver biopsies at regular intervals in order to identify

Table 2: Absolute and Relative Contraindications to Liver Transplantation

	Absolute	Relative
Age		>65 years-old
Neoplasms	Cholangiocarcinoma Hepatic Hemangiosarcoma Recent extrahepatic malignancies (non-remission, with oncological criteria)	
Extra-hepatic diseases	Severe or invalidating extra-hepatic diseases that do not improve with liver transplantation Hepatopulmonary syndrome with ppO2 <50mmHg. Severe pulmonary hypertension (PAP >45mmHg)	End-stage chronic renal failure
Infections	Severe extra-hepatic active infection at the time of transplantation. Uncontrolled HIV	Spontaneous bacterial peritonitis or cholangitis with less than 48 hour of therapy. HIV infection
Technical problems	Anatomic abnormalities precluding liver transplantation	
Psychosocial issues	Active drug or alcohol abuse Persistent non-compliance	
Special situations	Fulminant hepatic failure: Uncontrolled cerebral edema or multi-organic failure	

Table 3: The Child-Pugh Score*

Points	1	2	3
Encephalopathy	None	Minimal	Advanced
Ascites	Absent	Controlled	Refractory
Bilirubin (μmol/L)	<34	34–51	>51
Albumin (g/l)	>35	28–35	<28
Prothrombin time** (seconds)	<4	4–6	>6

*The score, corresponding to the sum of individual points, allows to categoriSe patients in Child-Pugh grades A (5–6 points), B (7–9 points) and C (10–15 points).
**Prothrombin time values of 4s and 6s correspond approximately to 50% and 40% of normal, respectively.

11. Villamil F G, "Hepatitis B: progress in the last 15 years", Liver Transpl *(October 2002);8(10 suppl. 1): S59–66.*
12. Roche B, Samuel D, "Prevention and treatment of hepatitis B virus infection after liver transplantation", Gastroenterol Clin Biol *(April 2005);29(4): pp. 393–404.*

progression to severe forms of chronic hepatitis. Several factors have been proposed to be associated with disease progression. The major determinant of accelerated progression is immunosuppression; however, global immunosuppression, not a single immunosuppressive agent, dominates the effect. In fact, the effect of specific immunosuppressive drugs on viral replication and disease progression is still unknown or controversial for most agents. The age of the donor has also been found to be independently associated with disease severity, disease progression and survival. Other factors associated with disease severity include viral load at transplantation, genotype and warming ischaemia time. The effects of live donor liver transplantation are still controversial. Antiviral therapy may be offered to these patients while awaiting the availability of an organ donor or following transplantation. Pre-transplantation therapy with PEGinterferon (PEG-IFN) (ribavirin is poorly tolerated and can precipitate worsening hepatic function and severe/life-threatening infections); however, if successful, HCV recurrence is generally prevented. The applicability of this approach is limited since only half the number of patients meet entry criteria, particularly with regards to thrombocytopenia and leukopenia. It is potentially a good option in selected patients (probably those with Child scores A) such as those with HCC. Post-transplantation therapy is aimed at achieving sustained viral suppression, which appears to be associated with an improvement in liver histology in most patients. It may be started pre-emptively during the first three weeks before histologic damage has occurred, or in the setting of recurrent disease. Treatment during the first weeks is seldom applicable due to the frequent development of side effects and the low proportion of patients meeting entry criteria, particularly with regards to anaemia, neutropenia and thrombocytopenia. Most of the published work on antiviral therapy has focused on the treatment of established disease.

Results with IFN or ribavirin as single agents have been disappointing. Efficacy is improved when both drugs are administered in combination for six to 12 months with overall sustained responses achieved in 9–33%. Severe side effects occur in a significant proportion of patients leading to frequent dose reductions or discontinuations, frequent hospital admissions and blood transfusions, frequent use of granulocyte colony-stimulating factor and erythropoietin and a constrained follow-up. The efficacy is higher when PEG-IFNs are used in combination with ribavirin. There are still several unanswered questions including the optimal duration of therapy, the best antiviral regime and the effectiveness of growth factors. With the available drugs, treatment of the established disease is probably the most cost-effective option. Although limited by a relatively low efficacy, tolerance appears to be better, and treatment is only offered to patients who develop progressive disease. In that sense, protocol liver biopsies may identify early histologic changes, which herald an aggressive course. Treatment should be initiated, if no contraindications are present, once portal fibrosis and/or moderate necroinflammation are detected.[13,14]

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases with excellent outcomes following liver transplantation, and survival rates of approximately 80% at five years. Both entities may recur following transplantation, with overall rates of 20% at five years of transplantation. The diagnosis is suggested by increased bilirubin and alkaline phosphatase levels, the development of pruritus, reappearance or increase of antimitochondrial antibody titres, or the development of other conditions believed to be autoimmune in nature. Confirmation of this diagnosis is complicated by the potential for concurrence of conditions that may mimic these diseases. The selection of a specific immunosuppressive regimen is still unclear. Therapeutic strategies for the prevention or treatment of recurrent PBC remain to be defined. In patients with PSC, therapeutic options for non-anastomotic strictures include radiologic or surgical therapies. Retransplantation may be considered in those with failing grafts. Both intermediate graft and patient survival rates are excellent and are unaffected by recurrent disease.[15,16]

Survival in patients undergoing transplantation for auto-immune hepatitis is excellent; however, recurrent disease may become an issue with prolonged follow-up, with an incidence ranging from 8% at one year to 60% after five years. Recurrence has not been linked to a specific immunosuppressive regimen. However, most studies have emphasised the hazards of discontinuing

13. *Berenguer M, "Natural history of recurrent hepatitis C",* Liver Transpl *(October 2002);8(10 suppl. 1): S14–18.*

14. *Charlton M, Wiesner R, "Natural history and management of hepatitis C infection after liver transplantation",* Semin Liver Dis *(2004);24 suppl. 2: pp. 79–88.*

15. *Neuberger J, "Liver transplantation for primary biliary cirrhosis: indications and risk of recurrence",* J Hepatol *(August 2003);39(2): pp. 142–148.*

16. *Bjoro K, Schrumpf E, "Liver transplantation for primary sclerosing cholangitis",* J Hepatol *(April 2004);40(4): pp. 570–577.*

17. *Gonzalez-Koch A, Czaja A J, Carpenter H A et al., "Recurrent autoimmune hepatitis after orthotopic liver transplantation",* Liver Transpl *(April 2001);7(4): pp. 302–310.*

immunosuppression, particularly steroids, as its reintroduction is frequently accompanied by improvement in liver function tests. Such biochemical response is not always associated with histologic resolution. A slow and careful tapering of immunosuppressive drugs, particularly prednisone, is therefore recommended. Graft and patient survival rates do not appear to be affected in the midterm.[17]

Alcoholic ESLD is a leading cause of ESLD and the second most common indication for liver transplantation worldwide. Initially, there were uncertainties about the outcome and concern for alcohol relapse. Although there are some factors that may identify those at risk of non-compliance, none has adequate sensitivity and specificity. The 'six-month abstinence' rule has become standard, although there is no evidence suggesting that a fixed period of abstinence will help identify those at risk of relapse; however, such a period of abstinence is helpful in defining patients whose liver function will improve. The one- and five-year actuarial survival rates after liver transplantation are 85% and 70%, respectively, in Europe, similar to those transplanted for non-alcoholic liver disease. In addition, post-transplant quality of life is not different from those who undergo transplantation for other causes of liver disease. Approximately 20% of transplanted patients do return to some pattern of alcohol consumption, although less than 5% damage their graft. Monitoring alcohol use and abuse is difficult; the measurement of carbohydrate deficient transferring may be useful. Liver transplantation in patients with acute alcoholic hepatitis had not been carried out in a systematic or protocolised fashion at the time of press.[18,19]

In conclusion, liver transplantation is now an established effective treatment to prolong survival and improve quality of life in patients with ESLD. The success of this therapy owes much to improvements in;

- the immunosuppressive regimes that prevent and suppress allograft rejection; and

- surgical techniques that diminish pre-operative complications.

Problems remain to be solved in the future, such as expanding the donor pool, for which marginal livers, split livers and live donors are already being used, developing selective, specific and relatively non-toxic immunosuppressive agents so that typical complications of these agents, including infections and cancer, can be reduced and developing and/or improving current agents to prevent and/or treat recurrent primary disease, particularly HCV and HCC. ■

18. *Neuberger J, Schulz K H, Day C et al., "Transplantation for alcoholic liver disease",* J Hepatol *(2002);36(1): pp. 130–137.*
19. *Lim J K, Keeffe E B, "Liver transplantation for alcoholic liver disease: current concepts and length of sobriety",* Liver Transpl *(October 2004);10(10 suppl. 2): S31–38.*