Liver transplantation

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Liver transplantation has evolved from an experimental procedure to an acceptable therapy for end-stage liver disease. The major challenges now faced are donor organ shortage, long-term complications related to immunosuppressive therapy, and the prevention and treatment of disease recurrence.

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It is almost 40 years since the first human liver transplantation was performed. The intervening years have seen dramatic advances in surgical technique, better organ preservation, improved recipient selection criteria and more specifically targeted immunosuppression. These and other improvements in postoperative patient care have led to dramatic improvements in graft and patient survival. Consequently, liver transplantation in the 21st century faces new challenges, those of donor shortages and disease recurrence in the liver transplant.

PATIENT SELECTION

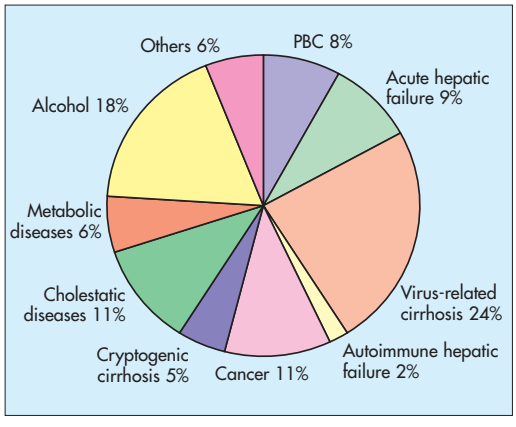
Liver transplantation is indicated for most causes of acute and chronic liver failure (*Table 1*). In Europe, the commonest indications are cirrhosis caused by hepatitis C virus (HCV) and alcohol (European Liver Transplant Registry, 2002) (*Figure 1*). The principal aims of liver transplantation are to prolong life and improve quality of life while optimizing the use of available resources. Currently there are more people waiting for liver transplantation than there are available donor organs (Pereira and Williams, 1998). Consequently, minimal criteria for placement of adults on the transplant waiting list have been defined (Neuberger and James, 1999). These recommend that patients should not be listed until their predicted 1-year survival is <90% while having an expected >50% 5-year survival with a transplant. The list of absolute contraindications to liver transplantation is diminishing (*Table 2*).

Many generic scoring systems for predicting survival in cirrhosis have been proposed but the most commonly used and easily applied remains the Childs–Pugh grading (*Table 3*). Cases for transplantation are usually grade B or C, although some cases with Childs–Pugh grade A disease and hepatoma are also transplanted. Survival is also significantly decreased after the development of variceal haemorrhage, spontaneous bacterial peritonitis or hepatorenal syndrome. Referral to a transplant centre should be

TABLE 1.
Indications for adult liver transplantation

Chronic liver disease	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Chronic viral hepatitis
	Alcoholic cirrhosis
	Autoimmune hepatitis
	Cryptogenic cirrhosis
	Budd–Chiari syndrome
Metabolic disease	Wilson's disease
	Haemochromatosis
	α1-antitrypsin deficiency
	Protoporphyria
Fulminant hepatic failure	Paracetamol poisoning
	Drug and toxin hepatotoxicity
	Acute viral hepatitis
	Wilson's disease
Malignancy	Hepatocellular carcinoma
	Epitheloid haemangiocarcinoma
	Neuroendocrine tumours

Figure 1. Indications for liver transplantation in Europe, 1998–2001 (European Liver Transplant Registry, 2002). PBC = primary biliary cirrhosis.



made before these complications ensue since early referral predicts a better outcome (Devlin and O'Grady, 1999). In order to facilitate early referral a number of disease-specific criteria are emerging based on specific risk scores such as those for primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) (Dickson et al, 1989, 1992). In patients with alcohol-related liver disease it is recommended that 6 months abstinence from alcohol is achieved before listing to provide time for recovery of any reversible element of the liver disease and possibly to reduce the rate of recidivism.

Liver transplantation is an important treatment option in the management of fulminant hepatic failure. The process of selecting appropriate patients is problematic. The King's College Hospital guidelines are often used, as they are applicable early in the hospital admission and use readily available parameters (O'Grady et al, 1989) (*Table 4*).

In cases with a hepatocellular carcinoma those with a single tumour less than 5 cm diameter or, where multiple, up to three lesions all less than 3 cm diameter and no evidence of vascular invasion have an acceptably low risk of tumour recurrence (Devlin and O'Grady, 1999).

OUTCOME

Outcome statistics are best assessed from studies of large numbers of patients such as that held at the European Liver Transplant Registry (European Liver Transplant Registry, 2002). Patient survival has improved steadily, with a 1-year survival rate for all indications of 79% in Europe in 1995 (*Table 5*). In selected cases, 1-year survival approaches 90%. Patients transplanted for cirrhosis have a better outcome than those transplanted for acute liver failure or malignancy (*Table 6*).

TABLE 2.
Contraindications to liver transplantation

Absolute	AIDS*
	Extrahepatic malignancy †
	Cholangiocarcinoma‡
	Advanced cardiopulmonary disease
	Active sepsis
Relative	HIV positivity*
	Age >70 years
	HBV DNA positivity§
	Active alcohol/substance misuse
	Severe psychiatric disorder
	Portal venous thrombosis¶
	Pulmonary hypertension¶

*With advances in antiretroviral therapy, human immunodeficiency virus (HIV) infection is now a relative rather than absolute contraindication. Acquired immunodeficiency syndrome (AIDS) remains an absolute contraindication. †Neuroendocrine malignancy is an exception in some centres. ‡Not an indication for transplantation because of high incidence of recurrence. §Most patients can be rendered hepatitis B virus (HBV) DNA negative with antiviral therapy. ¶Require assessment at a liver transplantation centre

IMMUNOSUPPRESSION

The development and evolution of immunosuppression acting at a variety of points in the pathway of immune activation of lymphocytes (*Figure 2*) has been pivotal in the growth of solid organ transplantation. Use of the calcineurin inhibitor cyclosporin increased 5-year

TABLE 3.
Childs–Pugh classification

Score	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	0	I/II	III/IV
Albumin (g/litre)	>35	28–35	<28
Bilirubin (mmol/litre)	<34	34–51	>51
Prothrombin time (seconds increased)	1–3	4–6	>6
Total	≤6	7–9	≥10
Class	A	B	C

TABLE 4.
King's College Hospital criteria for transplantation in acute liver failure

Paracetamol	pH <7.30 or	
	Prothrombin time >100 seconds, serum creatinine >300 mmol/litre and grade III/IV encephalopathy	
Non paracetamol	Prothrombin time >100 seconds or	
	Any three of the following	Aetiology: non-A, non-B hepatitis, halothane or other drug reaction
		Age <10 or >40 years
		Jaundice to encephalopathy >7 days
		Prothrombin time >50 seconds
		Serum bilirubin >300 mmol/litre

From O'Grady et al (1989)

TABLE 5.
Patient survival following liver transplantation

	Survival (%)	
Time post transplantation	1968–1988	1988–2001
1 year	53	79
5 year	41	69
10 year	37	61

From European Liver Transplant Registry (2002)

survival rates post liver transplantation from under 30% to over 70% (Iwatsuki et al, 1988). Tacrolimus, another calcineurin inhibitor, has comparable patient and graft survival statistics and may be associated with fewer and less severe rejection episodes (European FK506 Multicentre Liver Study Group, 1994). Both drugs have a significant side-effect profile (*Table 7*).

TABLE 6.
Post-transplant survival by diagnosis 1988–2001

	Survival (%)	
Indication	1 year	5 year
Acute hepatic failure	64	58
Alcoholic cirrhosis	83	72
Virus-related liver cirrhosis	81	69
Primary biliary cirrhosis	83	76
Autoimmune hepatic failure	81	72
Secondary biliary cirrhosis	73	69
Cancer	74	49

From European Liver Transplant Registry (2002)

Figure 2. T cell activation and site of action of immunosuppressive agents. IL-2 = interleukin 2.

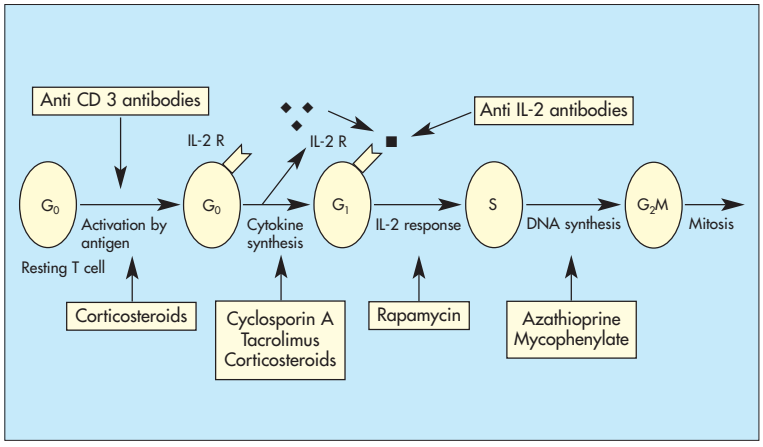


TABLE 7.
Side effects of commonly used immunosuppressive agents

	Cyclosporin	Tacrolimus	Sirolimus	Azathioprine	MM
Hypertension	+	+			+
Nephrotoxicity	+	+			
Neurotoxicity	+	+			
GI disturbance	+	+		+	+
Hyperglycaemia		+			+
Gingival hyperplasia	+				
Hypertrichosis	+				
Hyperlipidaemia			+		+
BM suppression			+	+	+

BM = bone marrow; GI = gastrointestinal; MM = mycophenylate mofetil

There is a lack of evidence on which to select optimal immunosuppression. Consequently, practice tends to depend on local experience. Regimens usually involve triple therapy with a calcineurin inhibitor, azathioprine and oral prednisolone. Liver transplant patients are particularly susceptible to the side effects of steroids, especially osteoporosis, therefore doses are kept low and therapy ideally discontinued after 3–6 months. Azathioprine is generally discontinued 12 months post transplantation. Thereafter, monotherapy with a calcineurin inhibitor is the mainstay of treatment. Disease-specific regimens are increasingly being used; lower doses for patients with viral hepatitis and higher doses for patients transplanted for autoimmune liver disease and patients who have had episodes of acute rejection.

Antilymphocyte monoclonal antibodies (ALG) have been used to treat steroid-resistant rejection and occasionally, in cases of renal impairment, they have been used in place of a calcineurin inhibitor. Owing to an association with post-transplant lymphoproliferative disorders, however, these drugs are used sparingly.

Recently, other immunosuppressive drugs have become available. Mycophenylate mofetil has been used in place of azathioprine to facilitate lower doses of calcineurin inhibitor, to reduce prednisolone usage and for steroid-resistant rejection. Rapamycin is evolving as an alternative to calcineurin inhibitors for use in poor renal function. Anti-interleukin-2 (IL-2) receptor antibodies (basiliximab and dacliximab) have been shown to reduce acute rejection in renal transplantation and are being assessed in clinical trials for liver transplantation.

COMPLICATIONS

Rejection

Acute, cellular rejection is common occurring in approximately 30–60% of allografts. It occurs early with a peak incidence 1 week post-transplantation. The clinical features are a deterioration in liver blood tests often with fever with high transaminases. Diagnosis is made by demonstrating a mixed inflammatory cell infiltrate on liver biopsy. Mild rejection may settle spontaneously, more severe disease usually responds to high dose corticosteroids (intravenous methylprednisolone 1 g on three successive days). Occasionally ALG may be required.

Chronic, ductopaenic rejection is less common, affecting 3–7% of transplants. It occurs later with a peak onset at 3 months. The presentation is with jaundice, itching, elevated alkaline phosphatase levels and histology showing a

paucity of bile ducts within portal tracts. No medical treatment is of proven benefit and patients may require a second transplant.

Post-transplant infection

Post-transplant infection is common with bacterial infection predominating. Cytomegalovirus (CMV) is a particular risk if a CMV-positive donor is used for a CMV-negative recipient. Infection may be generalized or organ specific, principally lung, liver and gastrointestinal tract. Early diagnosis is based on the detection of viral DNA by polymerase chain reaction. Treatment with ganciclovir is usually effective. Prophylactic use of ganciclovir in high-risk patients is of proven benefit (Stratta et al, 1991). Other viral infections are rarely a major clinical problem.

Local fungal infections are common and can be treated with topical therapy. Systemic infection is fortunately rare, usually occurring in hospitalized patients who are already very ill. Systemic candidiasis may be treated with fluconazole or amphotericin. Pulmonary or systemic aspergillosis requires amphotericin but is usually fatal. Pneumonia caused by *Pneumocystis carinii* is rarely seen as a result of effective prophylaxis with co-trimoxazole in those with lymphopaenia.

Disease recurrence

With advances in operative technique and improved treatment of infection and rejection, the problem of recurrence of the original liver disease has become an increasing threat to long-term graft survival. Patients transplanted for chronic hepatitis B virus (HBV) or HCV-related disease nearly always reinfect the new liver (Todo et al, 1991; Gane et al, 1996). For HBV, post-transplant therapy with intravenous immunoglobulin (HBIg) and lamivudine has reduced the incidence of disease recurrence and improved graft and patient survival (Samuel et al, 1993). This treatment is associated with the development of viral resistance and combination therapy with HBIg, lamivudine and adefovir may be required (Perrillo et al, 1999). HCV recurrence rarely causes graft loss in the first few years, but from 5 years accelerated graft fibrosis and loss is likely to be a problem (Prieto et al, 1999). Currently there is no satisfactory treatment for post-transplant HCV recurrence. Retransplantation is associated with a very poor outcome and is not recommended in most centres (Schluger et al, 1996).

Disease recurrence in PBC, PSC and autoimmune hepatitis is difficult to diagnose but occurs in up to 15% (Faust, 2000). While it does not appear to affect short-term graft survival, the long-term outlook remains unclear. The risk of recurrence of alcohol abuse remains an important issue despite efforts to screen candidates for abstinence before the transplant.

The risk of recurrent hepatic malignancy is determined by tumour pathology and size. As cholangiocarcinomas usually recur rapidly, they are not considered for transplantation. Patients with hepatomas <3–5 cm diameter have a good prognosis whereas those with larger tumours have poor survival (Stuart et al, 1996).

Long-term complications of immunosuppression

As patients survive longer, complications of long-term immunosuppression are becoming apparent. Vascular disease and renal impairment secondary to calcineurin inhibitors may develop in up to 30% of cases more than 7 years after transplantation. Hypertension and hyperlipidaemia are also common. Post-transplantation there is a high incidence of de novo malignancy, probably related to long-term immunosuppression (Fung et al, 2001). Epstein–Barr virus-associated lymphoma and virus-related skin cancers are especially prevalent. Long-term screening programmes are likely to be required.

HEPATIC RETRANSPLANTATION

In the current era of critical organ shortage, one of the most controversial questions facing transplant teams is whether retransplantation should be offered to a patient whose allograft is failing. *Table 8* shows that graft survival for second and subsequent transplants is inferior to that for first transplants. Models predicting survival for patients undergoing retransplantation are beginning to emerge. In the future it is likely that retransplantation will only be offered to candidates with low risk scores.

DONOR SHORTAGE AND POTENTIAL SOLUTIONS

The number of liver transplant operations performed in the UK has been increasing while the number of donor organs has remained static or

TABLE 8.
Graft survival according to re-transplantation 1988–2000

	Survival (%)		
Time post transplantation	First transplant	Second transplant	Third transplant
1 year	73	51	45
5 year	62	41	36

From European Liver Transplant Registry (2002)

decreased (Pereira and Williams, 1998). Consequently, unless the donor pool can be expanded, increasing numbers of patients will die waiting for a liver. Furthermore, it may become difficult to offer transplantation to patients with less favourable disease indications such as those with malignancy, acute liver failure and patients requiring retransplantation.

Current approaches to the organ shortage include efforts to encourage organ donation and the expanded use of current donors (Keefe, 2001). This has included the use of marginal donor livers such as those from older individuals and using livers with an element of fatty change. Split liver transplantation has been used to achieve liver transplantation in two recipients from a single cadaver liver; graft and patient survival rates of 88% and 90% respectively have been reported (Keefe, 2001). Living donor liver transplantation, originally adult to child but recently adult to adult, has been performed with excellent donor and recipient outcomes.

The shortage of human donor livers has led to increased interest in the field of xenotransplantation. Most attention is focused on the pig as a potential donor based on similar size and the ability to be genetically engineered to reduce tissue injury and rejection. There are still, however, considerable immunological hurdles to xenotransplantation and fears regarding transmission of novel infectious agents mean that this technique is still some way from clinical use. Hepatocyte transplantation has promise in the treatment of metabolic disorders when only a small number of cells may be required to achieve adequate function. Furthermore, in acute liver failure, hepatocyte transplantation may have the potential to replace lost hepatocytes or to prolong survival until there is recovery and regeneration of the injured liver. These and tools such as the bioartificial liver are being actively explored but are not yet clinically applicable.

KEY POINTS

- Liver transplantation is now a routine procedure with excellent early graft and patient survival.
- Too few donors are available for those awaiting transplantation.
- There are difficulties determining the optimal criteria for listing patients for transplantation.
- Early referral of potential candidates to transplant centres facilitates the timing and improves the outcome of transplantation.
- Early after transplantation, rejection and infection dominate postoperative complications.
- As patients survive longer, complications of long-term immunosuppression and recurrence of original disease dominate.

CONCLUSIONS

Liver transplantation is now a routine procedure with excellent short- and medium-term survival. One of the major challenges facing transplantation is the shortage of donor organs. Approaches to overcome this include use of marginal livers, splitting livers and the use of living related donations. Xenotransplantation and hepatocyte transplantation remain a distant possibility. Treatment and prevention of recurrent disease and immunosuppression-related complications is a major priority to optimize the use of liver grafts. HM

Conflict of interest: none.

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