Clinical Medicine 2011, Vol 11, No 2: 194–8

Liver transplantation: filling the gap between supply and demand

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Over the last two decades, the cirrhosis mortality rates have almost doubled in men and increased by half in women with cirrhosis mortality rates in Scotland being among the highest in Europe (45.2 per 100 000 men and 19.9 per 100 000 women in 2002)[1]; this corresponds with a 45% in the incidence of cirrhosis and 69% in prevalence during the decade 1991–2001, with an estimated 30 000 people living with cirrhosis and at least 7,000 new cases being diagnosed each year.[2]

Despite the many advances made in the management of patients with cirrhosis, transplantation remains the only definitive treatment for those with end-stage disease.

Liver transplantation (LT) is now a routine procedure with five-year survival of more than 70%.[3] However, there is a shortage of grafts: 15% listed patients die while awaiting a graft.[4] The number on the UK transplant list has trebled over the last 10 years while the availability of donor organs has increased only modestly (Fig 1).

Current indications and contraindications

The proportion of patients grafted for alcohol-related liver disease (ALD) and viral hepatitis (especially hepatitis C (HCV)) (Fig 2) is rising while the proportion of patients grafted for malignancy and cholestatic diseases is falling. Alcohol remains a controversial indication, although these patients have similar long-term outcomes to patients grafted for other indications (indeed, better than those grafted for HCV). Non-alcoholic fatty liver disease is increasing and is an increasing indication for LT.[7] Absolute contraindications are listed in Table 1.

Patient selection

Patients should be considered for selection if:

- the probability of survival without a transplant is less than survival with a transplant
- they have a survival probability of more than 50% at five years with an acceptable quality of life
- they have an unacceptable quality of life from the liver disease.

Criteria for selection are also designed to ensure that those patients who are listed will have a reasonable expectation of getting a graft – thus the size of the list does not reflect the need.

Assessment of prognosis

Several models have been developed to assess prognosis. The model for end-stage liver disease (MELD) score was initially developed to assess short-term prognosis following shunt procedures;[8] it is based on serum creatinine, serum bilirubin and the international normalised ratio. Additional points are given for liver cell cancer (>2 cm in diameter). The model has been validated in many clinical situations and different populations. However, there are concerns over reproducibility of some analytes and gender effects of creatinine.

The United Kingdom model for end-stage liver disease (UKELD), developed and validated for patients awaiting liver transplantation in the UK, contains the same variables as the MELD (although with different strengths) and serum sodium. A MELD score greater than 16 or a UKELD score above 49 indicate a survival benefit from transplant.

Selection criteria

The selection criteria for those with acute liver failure are shown in Table 2. For those with chronic liver disease, there are three categories for listing:

- projected one-year liver disease mortality without transplantation of over 9% (the current one-year survival after transplant is 91% in the UK)
- hepatocellular carcinoma (HCC) within agreed criteria
- variant syndromes (Table 3) LT.[9]

Liver allocation

At present, donated organs are allocated to one of the seven UK designated liver transplant centres. The centre's retrieval zone is adjusted to ensure equity of access. Allocation is determined by the centre, based primarily on ensuring optimal outcome rather than reducing mortality on the list. This policy is being reviewed. In the USA, minimal listing criteria were introduced, together with the creation of a 'Status 1' category (highest priority).[10]

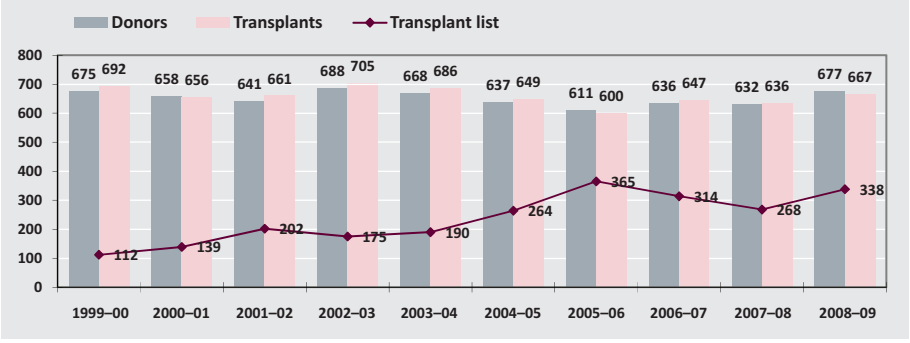

Fig 1. Deceased donor liver programme in the UK, 1 April 1999 to 31 March 2009 (adapted from NHS Blood and Transplant.[5])

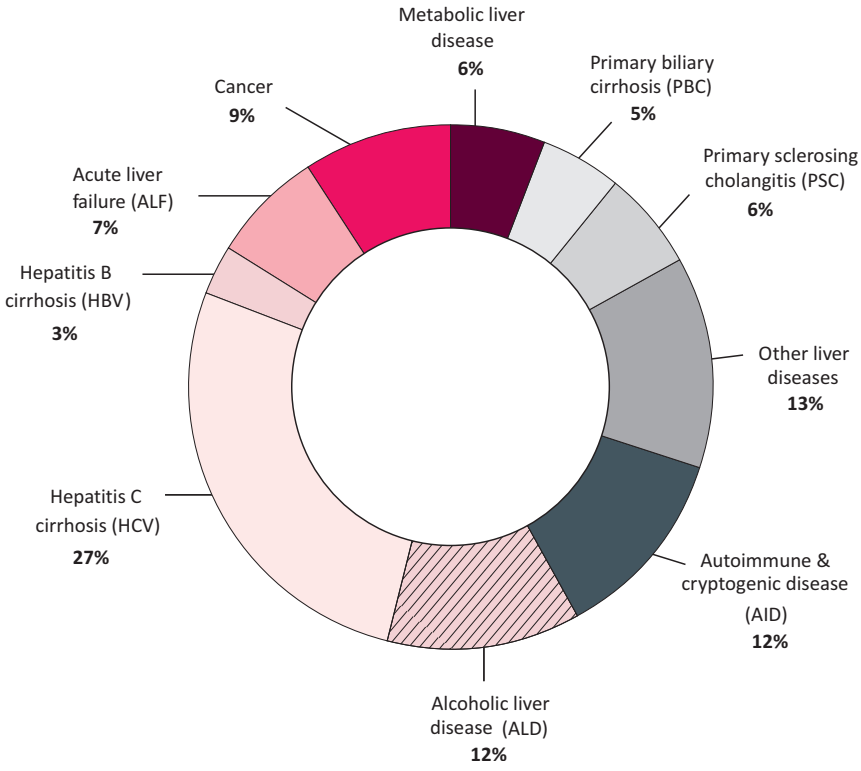

Fig 2. Indications for liver transplant (United Network for Organ Sharing (UNOS)).[6]

Table 1. Absolute contraindications to liver transplantation.

- Active extrahepatic malignancy.
- Active sepsis.
- Active alcoholism and uncontrolled substance misuse.
- Severe cardiopulmonary or other comorbid conditions compromising survival.
- Likely non-compliance that would not respond to suitable support.
- Technical reasons precluding transplantation (eg thrombosis of the entire portal and superior mesenteric venous system).

The Child–Turcotte–Pugh (CTP) scoring system was introduced as a semi-objective measure of disease severity; patients required a CTP score above 7. Because of the huge number of patients on the waiting list and, to reduce the waiting list mortality, a new system was introduced so that grafts were offered to the sickest patient first (as assessed by the highest MELD score).

Alcohol-related liver disease

Transplantation for ALD has been subject to much controversy. The UK Liver Advisory Group recommendations for liver transplantation in patients with ALD[11] include:

- an assessment by alcohol specialist
- signing an agreement indicating intention of abstinence before listing
- regular follow-up by alcohol specialist and transplant clinician in the pre- and post-transplant period.

Significant improvement is seen with abstinence.[12] Indeed with abstinence, many candidates referred for transplantation will improve to such an extent that transplantation is no longer indicated. There is no requirement for a fixed period of abstinence.

Current contraindications include:

- alcoholic hepatitis
- more than two episodes of medical non-adherence
- return to drinking after full professional assessment
- current illicit drug misuse.

The combination of ALD and HCV has a significant impact on the waiting list mortality as well as post-transplant mortality[13] and all HCV recipients are advised to abstain from alcohol.

Increasing the donor pool

Resources have been invested in increasing public awareness and donor rates are increasing slowly. The traditional donor pool is shrinking, in part because public health measures have been successful in reducing premature

Key points

The need for liver transplantation is increasing as mortality from liver disease is rising and outcomes after transplant are excellent

As a consequence of the shortage of donor livers, guidelines for selection and allocation have to be developed that are fair, just, equitable, transparent and, where possible, evidence-based

The traditional pool of donors is shrinking, so resources are prioritised to increasing awareness of organ donation, dispelling myths, and ensuring that all potential donors are identified and given the opportunity to donate their organs after death

The donor pool is being expanded by the use of donation after cardiac death, by using extended criteria donor grafts, by splitting livers to allow two recipients to receive organs from one donor, by increasing use of living donors and domino transplants

The success of liver transplantation in improving both the quality and length of life should not divert attention from the need to develop strategies for improving outcomes of those with acute and chronic liver disease

KEY WORDS: donation, liver transplantation

Table 2. Current UK blood and transplant criteria for registration as a super-urgent transplant: registered at UK Transplant, donor livers available from whole national pool. Adapted with permission from BMJ Publishing Group Ltd.[9]

Category	Aetiology	Criteria
1	Paracetamol poisoning	pH <7.25 more than 24 hours after overdose and after fluid resuscitation
2	Paracetamol poisoning	Co-existing PT >100 sec or INR >6.5, serum creatinine >300 mmol/l or anuria, and grade 3–4 encephalopathy
3	Paracetamol poisoning	Serum lactate >24 h after overdose >3.5 mmol/l on admission or >3.0 mmol/l after fluid resuscitation
4	Paracetamol poisoning	Two of the three criteria from category 2 with clinical evidence of deterioration (eg increased ICP, FiO2 >50%, increasing inotrope requirements) in the absence of clinical sepsis
5	Seronegative hepatitis, hepatitis A or B, or idiosyncratic drug reaction	PT >100 sec or INR >6.5 and any grade of encephalopathy
6	Seronegative hepatitis, hepatitis A or B, or idiosyncratic drug reaction	Any grade of encephalopathy, and any three of the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time>7 days, serum bilirubin >300 mmol/l, PT >50 sec or INR >3.5
7	Acute presentation of Wilson's disease or Budd-Chiari syndrome	Combination of coagulopathy and any grade of encephalopathy
8	Hepatic artery post-LT	Hepatic artery thrombosis on days <21 after liver transplantation
9	Early graft dysfunction post-LT	Early graft dysfunction on days 0–7 after liver transplantation with at least two of the following: AST >10,000 IU/l, INR >3.0, serum lactate >3 mmol/l, absence of bile production
10	Liver failure post living liver donation	Any patient who has been a live liver donor who develops severe liver failure within four weeks of the donor operation

AST = aspartate aminotransferase; FiO2= inspired oxygen concentration; ICP= intracranial pressure; INR = international normalised ratio; LT = liver transplantation; PT= prothrombin time.

death: for example, there are fewer deaths both from road accidents and from intracerebral trauma. Thus it is ever more important to encourage all potential donors to become actual donors.

Every allocation system has its own set of moral and ethical challenges. There is a need to balance the often conflicting demands of:

- equity: everyone has an equal opportunity of receiving a graft
- utility: allocation is determined by the best outcome
- benefit: where the survival benefits of transplant and non-transplant are compared
- justice, which implies a variety of benefits.

Public opinion

Public opinion is important but does not always reflect medically acceptable values. Surveys of the general public indicate that there is little support for transplantation using scarce organs for those with liver failure from overdose, alcohol or drug misuse.[14]

Individuals offer a variety of reasons for unwillingness to donate organs, including:

- lack of trust in the fairness of organ allocation
- uncertainties about the success of transplantation
- a belief that willingness to donate may affect their medical care
- concern of religious or cultural values.

It is important to retain public confidence in how organs from deceased donors are used. The development of agreed guidelines and protocols will ensure that those transplanted for ALD have a fair and just access to transplant. It is essential to ensure that patients with ALD and substance misuse understand and adhere to their role in the process.

Organ donation rates

Organ donation rates vary between countries for various reasons including cultural, ethical and legal. Donation rates in the UK, although rising, continue to be lower than in Spain which has the highest donation rate. The Spanish model, introduced in 1989, is based on a decentralised network of specifically trained transplant coordinators (most of them physicians working in intensive care units) with organ procurement as the main goal.[15]

The Spanish model has been broadly adopted in the UK with a significant injection of resources and the introduction of several initiatives. These include the introduction of a national body of nearly 250 donor transplant coordinators (specialist nurses in organ donation), clinical leads in organ donation, donation committees in all acute hospitals and a national organ retrieval service. The main focus of the work is to ensure that all potential donors are identified, brain stem death testing applied where appropriate, and the individuals and the families of all those where donation is possible are given the opportunity to donate.

Consent

The laws governing consent (or authorisation) are clearly defined and regulated by professional bodies and the Human Tissue Authorities. The debate about the benefits of opt-in and opt-out systems

Table 3. Variant syndromes and definitions for selection to the adult elective liver transplant waiting list . Adapted with permission from BMJ Publishing Group Ltd.[9]

Variant syndrome	Selection criteria
Diuretic resistant ascites	Ascites unresponsive to or intolerant of maximum diuretic dosage and non-responsive to TIPSS, or where TIPSS deemed impossible or contraindicated and in whom the UKELD score at registration is ⩽49
Hepatopulmonary syndrome	Arterial PO2 <7.8 kPa, alveolar-arterial O_2 gradient <20 mmHg, calculated shunt fraction >8% (brain uptake following technetium macro-aggregate albumin), pulmonary vascular dilatation documented by positive contrast enhanced transthoracic echo in the absence of overt chronic lung disease
Chronic hepatic encephalopathy	Confirmed by electroencephalogram (EEG) or trail making tests with at least two admissions in one year due to exacerbations of encephalopathy that have not been manageable by standard therapy. Structural or neurological disease must be excluded by appropriate imaging and, if necessary, psychometric testing
Persistent and intractable pruritus	Pruritus consequent on cholestatic liver disease intractable after therapeutic trials which might include cholestyramine, ursodeoxycholic acid, rifampicin, ondansetron, naltrexone and, after exclusion of psychiatric comorbidity that might contribute to the itch
Familial amyloidosis	Confirmed transthyretin mutation in the absence of significant debilitating cardiac involvement or autonomic neuropathy
Primary hyperlipidaemias	Homozygous familial hypercholesterolaemia with absent LDL receptor expression and LDL receptor gene mutation
Polycystic liver disease	Intractable symptoms due to the mass of liver or pain unresponsive to cystectomy or severe complications secondary to portal hypertension

LDL = low density lipoprotein; TIPSS = transjugular intrahepatic portosystemic shunt; UKELD =United Kingdom model for end-stage liver disease.

continues. The UK has opted, for the present time, to remain with the opt-in process. Other health administrations have adopted different approaches, including giving priority for receipt of organs to those who have agreed to donate. There is now clarity over the diagnosis of death and the appropriateness of interventions to allow donation to proceed and fulfil the wishes of the individual to donate.

The Organ Donor Register (ODR) allows people to indicate their willingness to donate and indicate which organ or tissue they would wish to donate in the event of their death. There are currently over 17 million people registered on the ODR.

Expansion of the donor pool

Extended criteria donors (ECDs) are defined as those having characteristics that increase the probability of graft failure or disease transmission compared with the lower risk standard criteria donors. Characteristics of ECD liver grafts include increasing steatosis, donor age and length of intensive therapy unit (ITU) stay. Other factors that may make a graft at higher risk to the recipient include positive hepatitis, HIV serology and a history of malignancy. These factors will be exacerbated by prolonged cold ischaemia times.

Organs from patients with donation after cardiac death (DCD) (also known as non-heart beating donors) offer the potential to increase the donor pool to the conventional donation after brain death (DBD) (also known as brain-stem death donors). There are several classes of DCD patients. Those who are controlled donors (where death occurs after planned withdrawal of treatment) offer a significant increase of the donor pool. Such donors may come not only from the ITU but also from emergency medicine departments.

It is a tribute to surgical skills that outcomes are not deteriorating, even though the overall number of high-risk donors is increasing. In general, outcomes of organs from DCD donors are inferior to those of DBD donors, but this difference is being reduced with increasing experience. There still remain concerns about the longer-term outcomes, particularly with respect to ischaemic biliary strictures.

Surgical approaches to increase the donor pool

Living donation

Living donor transplantation can expand the donor pool, especially in those areas such as Asia where deceased donation rates are very low. The risks to the donor remain a concern, with reported mortality of up to one in 250 for adult-to-adult donation (the risks are less for left lobe donation).[16]

Split liver

Two grafts are generated from one donor liver. The most widely used technique is to split the graft into left lateral sectoral graft (segments 2 and 3) for a child and a right trisegmental graft (segments 1 and 4–8) for an adult. Various splitting techniques have been described. Irrespective of the technique used, outcomes seem to be comparable with deceased donor grafts.

Auxiliary transplants

Auxiliary liver transplantation is a technique in which all or part of the graft is placed in the abdomen and the native liver left in situ. This procedure will not increase the donor pool but is an option for those in whom there is a potential for recovery of the native liver. If the native liver recovers, immunosuppression may be withdrawn.[17]

Domino liver transplantation

In this technique the explanted liver is grafted to another. Livers from a handful

of metabolic disorders (such as porphyria or amyloid), cured by liver transplantation, are used for domino transplantation. The genetic disorder either manifests later in life of the recipient or never manifests.

Xenotransplantation

Although xenotransplantation (animal to human) was performed initially in 1966, this remains, as it has always been, an option for the future. It is currently illegal.

New developments

1 Machine-based liver preservation and newer perfusion fluids may allow greater use of marginal livers and improve their chance of good function.
2 Liver support devices have been developed which may bridge an ill patient in liver failure to transplant or allow time to spontaneous recovery.
3 Hepatocytes and stem cell transplantation are being intensively evaluated and offer some promise.

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Corrigendum

D'Arcy J, Myerson SG. Investigations in valvular heart disease. *Clin Med* 2010;10:172–6.

Please note that Dr Myerson and Dr d'Arcy would like to acknowledge support from the Oxford NIHR Biomedical Research Centre programme in relation to this article.

CME Geriatric medicine SAQs

Answers to the CME SAQs published in *Clinical Medicine* February 2011

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
(d)	(c)	(e)	(c)	(d)	(c)	(c)	(b)	(c)	(e)