

**NHS BLOOD AND TRANSPLANT  
LIVER ADVISORY GROUP**

**Protocols and Guidelines for Adults Undergoing Deceased Donor  
Liver Transplantation in the UK**

**PROTOCOLS AND GUIDELINES**

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# PROTOCOLS AND GUIDELINES

## Summary

There remains a gap between the number of patients suitable for liver transplantation and the number of donated human livers so that decisions on selection of patients for liver transplantation have to be made on criteria other than just medical need. Following the death of a young woman with liver failure, a colloquium was set up in 1999 to discuss guidelines for selection of patients for transplantation and attended by transplant clinicians, patient representatives, health care professionals and medical ethicists. This paper combines the results of that colloquium with other extant guidance on the allocation of donor livers.

It was agreed that livers donated for transplantation should be considered a national resource and therefore guidelines for their use needed to be agreed publicly and followed nationally. Patients should be considered for transplantation if they had an anticipated length of life (in the absence of transplantation) of less than one year or an unacceptable quality of life. Patients should be accepted for transplantation only if they had an estimated probability of being alive five years after transplantation of at least 50% with a quality of life acceptable to the patient. Should the patient's condition deteriorate whilst waiting for a liver so that these criteria are no longer met, the patient should be removed from the list. Other medical and social factors (such as alcohol or drug misuse, age or antisocial life style) are not directly relevant other than whether they affected the above criteria; implementation of these guidelines should be left to those responsible for the care of the patient. As with any guidelines, there needs to be continued re-assessment and modification.

The full guidelines produced from the colloquium, and accepted as the basis for assessing patients for liver transplantation by the Directors of Liver Transplant Centres in the UK, were published in the Lancet.<sup>1</sup>

More recently a working group was set up by the Liver Advisory Group of NHS Blood and Transplant (NHSBT) to examine equity of access in liver transplantation and to make recommendations about selection for the transplant list and allocation of donors to patients thus selected. Equity was defined as each patient within defined categories having an equal chance of being accepted onto a national transplant list and a similar chance of dying on the list or receiving a graft irrespective of where they live and to which centre they are referred. This culminated in two Consensus Conferences on transplantation for Acute and Chronic Liver Diseases and transplantation for Hepatocellular Carcinoma. These recommendations were accepted at the Liver Advisory Group meetings of May 2007<sup>2</sup> and May 2008<sup>3</sup>.

This document considers transplantation into adult patients of whole or split deceased donor livers and for elective and super-urgently listed patients. At the present time, selection criteria for live donor liver transplantation have been agreed to be similar to deceased donor liver transplantation.<sup>4</sup>

## September 2009

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<sup>1</sup> Guidelines for selection of patients for liver transplant in an era of donor organ shortage: 199 vol 354 (910): 1636-1639.

<sup>2</sup> Minutes of the eleventh meeting of the NHSBT Liver Advisory Group, 23 May 2007, LAG(M)(07)1.

<sup>3</sup> Minutes of the thirteenth meeting of the NHSBT Liver Advisory Group, 14 May 2008, LAG(M)(08)1.

<sup>4</sup> National standards for live donor liver transplantation.

## PROTOCOLS AND GUIDELINES

### 1 Introduction

- 1.1 The transplant specialty within the NHS is relatively new: liver transplants have a shorter history than the specialty as a whole. All forms of transplantation do, however, carry certain common features: with the exception of kidney failure for which dialysis is an option, it is the only treatment available in the case of major vital organ failure; it is also entirely dependent upon a source of donor organs which is outside the control of clinicians or commercial suppliers. Although developments in cell growth techniques and xenografting give rise to hope, these are for the future. The following guidelines are intended to apply to the use of deceased donor livers (whole or split) but not to livers from living donors.
- 1.2 As with most emerging specialities, the number of patients who could benefit from the treatment has changed over the years and transplant lists have risen in recent years. Equally, research and development has ensured that outcomes in terms of survival have increased to a remarkable degree.
- 1.3 The supply of donor organs is a limiting factor and one which has resulted in the development of a national organ sharing scheme to ensure equality of access to treatment throughout the NHS. The rapid increase in the number of patients with disorders which may benefit from transplantation and 'diagnosed' as suitable for transplantation has not been matched by the availability of donor organs. In recent years research and development by transplant centres extended the margins and has increased the proportion of available organs, which are useable. Splitting livers has, in some cases, also been possible so as to increase the organ transplants available; similarly, living lobe donation has also provided a transplant for a few patients. Non-heartbeating donors also provide suitable grafts.
- 1.4 A high level of co-operation is necessary UK-wide between centres and exists to ensure the retrieval of all possible available organs. The surgical technique for transplanting organs and associated skills has been developed in order to use a higher proportion of retrieved organs. Also, their rapid and efficient use, with sharing based on equitable protocols, which are agreed by the profession nationwide, is needed.
- 1.5 Associated with the increased success of transplants is an increased length of survival for transplant patients, coupled with groups of higher risk patients being treated. Such protocols must balance the often-competing issues of equity of access for all with overall utility (or benefit in outcome). Higher levels of skills are now required in assessing

patients prior to their being placed on the transplant list, and in their post-transplant maintenance and follow-up.

- 1.6 In 2007 an Organ Donation Taskforce was set up under the Chairmanship of Elisabeth Buggins, and reported in 2008. A number of recommendations were made with respect to the organisation of donor services with the aim of increasing donation rates by 50% over 5 years. Changes to the provision of organ donation services include the development of over 250 donor transplant co-ordinators, embedded in hospitals but managed by the Organ Donation and Transplantation Directorate of NHSBT and the development of a national retrieval service.

## 2 The need for transplantation

- 2.1 Referral to a transplant centre - Most patients with liver disease are not managed in transplant centres. Patients referred for assessment for liver transplant will include those with the following broad categories of conditions.

### PRIMARY RECIPIENT DISEASE

Cirrhosis:	Alpha - 1-antitrypsin deficiency
Primary biliary cirrhosis	Budd-Chiari syndrome
Secondary biliary cirrhosis	Wilson's disease
Cryptogenic	Biliary atresia
Alcoholic	Other congenital biliary abnormalities
Non-alcoholic fatty liver disease	Acute/subacute fulminant hepatic failure (FHF)
Chronic active hepatitis (autoimmune)	Primary hepatocellular cancer in cirrhotic liver
Chronic viral hepatitis B	Cystic Fibrosis
Chronic viral hepatitis C	Polycystic liver disease
Congenital hepatic fibrosis	Familial Amyloidosis syndromes
Primary sclerosing cholangitis	Inborn errors of metabolism not in CLF group
Secondary sclerosing cholangitis	

- 2.2 The indications for transplantation are usually accepted to be either an unacceptable quality of life (because of liver disease) or anticipated length of life without transplantation that is shorter than that with transplantation. For many conditions there are clinical guidelines and algorithms to help the clinician decide whether a patient meets either of these criteria: patients meeting either of these should be offered a transplant only if the clinician feels that they have a greater than 50% probability of survival at 5 years after transplantation with a quality of life that is acceptable to the patient. Thus outcome criteria become an integral factor in the selection process. The British Society of Gastroenterology has published guidelines on the indications for

referral and assessment in adult liver transplantation<sup>5</sup> and more recently the results from a consensus conference organised under the auspices of The British Association for the Study of the Liver and the British Transplant Society were published.<sup>6</sup>

### 3 Assessment

- 3.1 Assessment is carried out by the transplant multi-disciplinary team. It is usually desirable for the patient's family to be involved in the assessment process. These initial assessment procedures often follow outpatient review and consultation and are undertaken over several days; patients remaining on the transplant list will be re-assessed at intervals during their wait for a donor organ.
- 3.2 The decision whether or not to register a patient on the transplant list will be made after discussion with the patient and other relevant healthcare professionals, including anaesthetists, transplant coordinators and psychiatrists. The patient's family and partner usually will be involved as patients find that helpful and the family's support is likely to improve the eventual outcome. Other factors which will need to be considered will include the reason which gave rise to the primary cause of liver failure (for example, alcohol-induced liver diseases); a history of illegal drug use or of self-inflicted; medical or psychiatric conditions; and the patient's age. These are discussed briefly below.
- 3.2.1 **Alcohol-induced liver disease:** A history of excess alcohol is relevant in regard to potential or actual significant damage to cardiovascular and neurological tissue, or to the risk that patients might revert to alcohol abuse or might not comply with medication or follow up schedules and thus damage the new liver. A multi-disciplinary approach is required to select patients who are likely to comply with follow-up and not return to a damaging pattern of alcohol consumption after transplantation and may include psychological/psychiatric assessment. Appropriate follow-up strategies may be needed.<sup>7</sup>
- 3.2.2 **Illicit drug use:** Is not a contraindication to transplant if the patient will comply with the required management schedules. However, continued intravenous drug use is considered a contraindication owing to the possible risk of infection in an immune-suppressed patient.<sup>8</sup>

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<sup>5</sup> A clinical guide (Devlin J, O'Grady J, Gut 1999;45;suppl 6; vi1-vi22

<sup>6</sup> Selection of patients for liver transplantation and allocation of donated livers in the UK. Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, Hudson M; Liver Advisory Group; NHSBT. Gut. 2008 Feb;57(2):252-7.

<sup>7</sup> NHSBT Liver Advisory Group: Recommendations for Liver Transplant Assessment in the context of Alcohol-related Liver Disease.

<sup>8</sup> NHSBT Liver Advisory Group: Recommendations for Liver Transplant Assessment in the Context of Illicit Drug Use.

- 3.2.3 **Age:** In itself is not a contraindication, although the survival rate after transplantation in the over 65s is significantly worse than that of younger patients.
- 3.2.4 **Self-inflicted conditions:** Such as resulting from an overdose of paracetamol would only be contraindicated if there were good reason to believe that the patient would, despite appropriate support, return to a behavioural pattern that would lead to liver failure or result in a quality of life unacceptable to the patient. The views of the family doctor and other support agencies and the family may have to be taken into account.
- 3.2.5 **Medical and psychiatric conditions:**
- 3.2.5.1 Concurrent extra-hepatic co-morbid medical or psychiatric conditions are relevant if they will affect the patient's quality of life or prospect for survival post-transplant. Where uncertainty remains, evaluation should be considered in discussion with other transplant centres and, where appropriate, the Associate Medical Director of NHSBT/Chairman of NHSBT Liver Advisory Group.
- 3.2.5.2 Patients in whom early graft damage from recurrent disease can be anticipated should only be transplanted as part of an agreed protocol of treatment. There are well-developed local protocols now to prevent or treat the effects of recurrent HCV and HBV infections but problems remain with hepatic malignancy.
- 3.2.5.3 With the advent of effective treatment, those co-infected with the HIV may be suitable candidates for transplantation.
- 3.2.6 **Regrafts:** Will need special consideration dependent on the circumstances which gave rise to the need for regraft, as results after early regraft are poor and only limited benefit may be achieved. However, the principles that apply to primary grafts should also apply to regrafts.
- 3.2.7 **Malignancy:** Where potential liver allograft recipients have suffered from previous extrahepatic malignancy, the decision to proceed for liver transplantation should depend, in part, on the probability of malignancy recurring and failing to respond to treatment following liver transplantation. Some immunosuppressive agents may encourage the growth of malignancy. Patients should be considered in the light of section 2.2. Selection criteria for patients with primary hepatic malignancy are considered below. Cholangiocarcinoma and secondary hepatic malignancy are not appropriate indications for transplantation.

- 3.3 It also has to be recognised that patients awaiting a liver transplant are, by definition, ill and their condition may deteriorate to the extent that the probability of a 5-year survival may fall below 50%. In these circumstances, the patient will be removed from the transplant list but only after full discussion with them. Such patients - although in greatest need - are at greatest risk of not benefiting after transplantation.

## 4 Selection criteria

### 4.1 Adult (aged 17 years and older) liver transplantation

An individual can be considered either for a super-urgent liver transplant when they have the most severe form of liver disease or an elective liver transplant.

#### 4.1.1 Super-urgent liver transplantation

To be registered on the super-urgent liver scheme, at least one of the following criteria must be met:

- 4.1.1.1 **Aetiology: Paracetamol poisoning:** pH <7.25 more than 24 hours after overdose and after fluid resuscitation.
- 4.1.1.2 **Aetiology: Paracetamol poisoning:** Co-existing prothrombin time >100 seconds or INR >6.5, and serum creatinine >300 µmol/l or anuria, and grade 3-4 encephalopathy.
- 4.1.1.3 **Aetiology: Paracetamol poisoning:** Serum lactate more than 24 hours after overdose >3.5 mmol/l on admission or >3.0 mmol/l after fluid resuscitation.
- 4.1.1.4 **Aetiology: Paracetamol poisoning:** Two of the three criteria from category 2 with clinical evidence of deterioration (eg increased ICP, FiO<sub>2</sub> >50%, increasing inotrope requirements) in the absence of clinical sepsis.
- 4.1.1.5 **Aetiology:** Seronegative hepatitis, hepatitis A or hepatitis B, or an idiosyncratic drug reaction. Prothrombin time >100 seconds or INR >6.5, and any grade of encephalopathy.
- 4.1.1.6 **Aetiology:** Seronegative hepatitis, hepatitis A or hepatitis B or an idiosyncratic drug reaction. Any grade of encephalopathy, and any three from the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time >7 days, serum bilirubin >300µmol/l, prothrombin time >50 seconds or INR >3.5.

4.1.1.7 **Aetiology:** Acute presentation of Wilson's disease, or Budd-Chiari syndrome. A combination of coagulopathy, and any grade of encephalopathy.

4.1.1.8 **Hepatic artery thrombosis** on days 0 to 21 after liver transplantation.

4.1.1.9 **Early graft dysfunction** on days 0 to 7 after liver transplantation with at least two of the following: AST >10,000, INR >3.0, serum lactate >3 mmol, absence of bile production.

4.1.1.10 **Liver failure after live liver donation.**

#### 4.1.2 **Elective liver transplantation**

Patients can be considered for elective transplantation if they have an anticipated length of life or survival in the absence of transplantation that is less than that obtained with a liver transplant, or an unacceptable quality of life. Patients are accepted for elective transplantation if they have an estimated probability of being alive 5 years after transplantation of at least 50% with a quality of life acceptable to the patient and if they are eligible to receive a transplant in the UK. (*ref EU eligibility document when available*).

To be registered on the elective liver transplant list, adult patients awaiting a first liver transplant must meet at least one of the following four criteria.

- Chronic liver disease or failure.
- Hepatocellular carcinoma.
- A variant syndrome.
- Have been accepted through the National Appeals Panel (see 4.1.2.4).

##### 4.1.2.1 **Chronic liver disease or failure**

The patient has a projected one-year liver disease mortality without transplantation of >9%, predicted by a UKELD score of 49 or greater. The UKELD score is derived from the patient's serum sodium, creatinine and bilirubin and International Normalised Ratio of the prothrombin time (INR).

Patients with alcoholic liver disease, past intravenous drug use or current methadone users must be assessed

as recommended in Liver Advisory Group documents.<sup>910</sup> Professional assessment of the risk of recurrence of at risk behaviour will be undertaken and either a contract signed by the patient or a letter sent from the transplanting centre stating the criteria on which transplantation is offered, the contents of which are agreed with the patient. Patients are strongly advised to stop smoking prior to any transplant

Patients with porto-pulmonary syndrome (mean PAP  $\geq$  35mmHg,  $<$  50mmHg; PVR  $\geq$  120 dynes.s.cm<sup>-5</sup>; PCWP  $<$  15mmHg), should have a clinically significant response to one of lanoprost, sildenafil or bosentan. Porto-pulmonary syndrome is not considered a variant syndrome.

#### 4.1.2.2 Hepatocellular cancer

Radiological assessment should include both MDCT and MRI with size being assessed by the widest dimensions on either scan. A tumour (for the purposes of counting numbers) will require to be identified as an arterialised focal abnormality with portal phase washout on MDCT or Gd enhanced MR. Other tumours are considered indeterminate and do not count. Tumour rupture and an AFP  $>$ 10,000 iu/ml are absolute contraindications to transplantation, as are extrahepatic spread and macroscopic vascular invasion.

The following are criteria for listing for transplantation:

- a single tumour  $\leq$  5cms diameter or
- up to 5 tumours all  $\leq$  3cms or
- single tumour  $>$ 5cms and  $\leq$ 7cms diameter where there has been no evidence of tumour progression (volume increase by  $<$ 20%) and no extrahepatic spread and no new nodule formation over a 6 month period.

Locoregional therapy +/- chemotherapy may be given during that time. Their transplant list place may be considered from the time of their first staging scan.

Locoregional therapy should be considered for all transplant list patients who have an hepatocellular carcinoma.

Patients outwith current proposed selection criteria will not be selectable on to the transplant list after their tumour has been downsized by surgical or locoregional treatments.

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<sup>9</sup> NHSBT Liver Advisory Group: Recommendations for Liver Transplant Assessment in the Context of Illicit Drug Use.

<sup>10</sup> NHSBT Liver Advisory Group: Recommendations for Liver Transplant Assessment in the context of Alcohol-related Liver Disease.

#### 4.1.2.3 A variant syndrome

A patient can have more than one variant syndrome.

- a) **Diuretic resistant ascites** - Ascites unresponsive to or intolerant of maximum diuretic dosage and non-responsive to TIPS or where TIPS deemed impossible or contraindicated.
- b) **Hepatopulmonary syndrome** - Arterial  $PO_2 < 7.8$ , alveolar arterial oxygen gradient  $> 20$  mmHg, calculated shunt fraction  $> 8\%$  (brain uptake following TC macroaggregated albumen), pulmonary vascular dilatation documented by positive contrast enhanced transthoracic echo, in the absence of overt chronic lung disease.
- c) **Chronic hepatic encephalopathy** - Chronic hepatic encephalopathy confirmed by EEG or trail making tests, with at least two admissions in one year due to exacerbations in encephalopathy, not manageable by standard therapy. Structural neurological disease must be excluded by appropriate imaging and, if necessary, psychometric testing.
- d) **Persistent and intractable pruritus** - Pruritus consequent on cholestatic liver disease which is intractable after therapeutic trials. Exclude psychiatric co-morbidity that might contribute to the itch. Lethargy is not an accepted primary indication for orthotopic liver transplantation.
- e) **Familial amyloidosis** - Confirmed transthyretin gene mutation in the absence of significant debilitating cardiac involvement, or autonomic neuropathy.
- f) **Primary hyperlipidaemia** - Homozygous familial hypercholesterolaemia, absent LDL receptor expression and LDL receptor gene mutation.
- g) **Polycystic liver disease** - Intractable symptoms due to mass of liver or pain unresponsive to cystectomy, or severe complications secondary to portal hypertension.

- h) **Recurrent cholangitis** - Recurrent significant cholangitis not responsive to medical, surgical or endoscopic therapy.
- i) **Other** - Any other type of variant syndrome not included in a) to h) above, as agreed by a national selection panel.

#### 4.1.2.4 National Appeals Panel

If a centre wishes to register an adult patient for an elective first liver transplant who does not satisfy at least one of the criteria of chronic liver disease, hepatocellular carcinoma or a variant syndrome, a request should be made in writing to members of the National Appeals Panel. The Appeals Panel is constituted of one physician or surgeon from one centre within each of the three regions; North (Leeds, Newcastle, Edinburgh Liver Transplant Centres); Central (Birmingham, Cambridge Liver transplant Centres); Southern (Royal Free, Kings Liver Transplant Centres). They will seek the views of colleagues in their region. Decisions have to be unanimous; if not unanimous then further information about the patient may be provided to the Appeals Panel so a more informed decision can be made. Members of the panel will respond with a decision when possible within five working days of the request.

#### 4.1.2.5 Other criteria

a) **Retransplantation** - Registrations for second or subsequent transplants are not subject to these criteria and decisions are at the discretion of each transplant centre. Re-transplants are only undertaken when there is evidence of irreversible graft failure and the risk of mortality from that exceeds the slightly increased post operative mortality after re-transplantation.

b) **Multivisceral transplantation** - Rarely liver transplantation is undertaken with one or more other organs such as kidney, pancreas or small bowel. Simultaneous kidney and liver Transplantation is only undertaken when there is evidence of kidney failure which will not recover with a liver transplant alone. In the case of adult multivisceral transplants including intestine, these are only undertaken in one centre (Cambridge). Adult transplantation of intestine alone occurs in two Centres (Cambridge and Oxford) and is undertaken when there is evidence of intestinal failure

not satisfactorily manageable by continuous parenteral (intravenous). All adult patients for these procedures are discussed at a National Forum that includes gastroenterologists, hepatologists and transplant surgeons.

c) **Live-donor liver transplantation** - The indications for a live donor liver transplant are identical to those for super-urgent and elective liver transplantation from deceased organs.

d) **Domino liver transplantation** - Rarely a transplant is performed when the liver being removed has a genetic defect in a single enzyme, but is otherwise normal. In some circumstances that removed liver can be used for transplantation – domino transplantation. Each transplant centre may decide which patients are most acceptable to receive such an organ. In these circumstances full informed consent from the recipient must be obtained including discussion about the risk and side-effects of de-novo disease appearing consequent on using an organ with such genetic defects.

## 4.2 Paediatric (aged 16 years and under) liver transplantation

4.2.1 Paediatric (patients aged 16 years and under) liver transplantation is covered in a separate document.

## 5 Patient registration

5.1 Patients can be placed on a UK transplant list only following registration with NHSBT. Patients who have not been registered should not be offered an organ. Patients are required to consent to transfer of their data onto the UK Transplant Registry, which is maintained by NHSBT on behalf of transplant services in the UK and holds detailed information about each patient awaiting any organ transplant in order that they may have an up to date status of the state of the transplant list.

## 6 Allocation of donor livers

6.1 The principles through which donor livers will be allocated are discussed and agreed through the NHSBT Liver Advisory Group network. Copies of the protocol<sup>11</sup> (which is updated from time to time) are available from NHSBT.

6.2 Currently donors are allocated to centres as described in the Donor Organ Sharing Scheme; Operating Principles for Liver Transplant

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<sup>11</sup> Donor Organ Sharing Scheme. Operating Principles for Liver Transplant Centres in the UK and Republic of Ireland. Prepared by the NHSBT Liver Advisory Group.

Centres in the UK and are updated regularly. These guidelines do not specify which patient to select when a liver suitable for more than one patient becomes available. There may be many factors such as the quality and size of the liver and blood group, the health of the patient and pressures on beds and staff, which will influence the choice of recipient. A number of general principles are relevant; patients with equal UKELD scores should be prioritised on the basis of length of time they have waited. When equal post-transplant outcome is anticipated then the sicker patient would normally be transplanted first; the impact of specific donor characteristics on recipient outcome post-transplant should always be considered. These guidelines do not help the clinician decide between two recipients or to decide whether a liver should be transplanted into a patient who is dying from end-stage liver disease or into a patient with an intolerable quality of life (for example, because of intractable itching). A patient's contribution to society or ability to pay must never be factors taken in to consideration when allocating donors.

- 6.3 The decision whether a liver should be transplanted into an individual should take account of both recipient and donor factors. Where possible the donor should be matched to the recipient who is expected to obtain the largest transplant benefit from the procedure (difference between survival with and without transplantation).
- 6.4 When there is a potential for conflict of interest, for example when the surgeon or Institution has received or may receive any benefit for transplanting any potential recipient for a liver graft, there should be mechanisms in place to ensure that there is an independent, objective and transparent basis for allocation.

## 7 Conclusion

The imbalance between donor supply and need for liver transplantation is likely to grow further. Inevitably clinicians will face complex issues and should be encouraged to discuss them openly in a multi-disciplinary team environment, which encompasses the views and needs of patients who should have every opportunity to express their concerns.

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