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Adult liver transplantation in the United Kingdom (I): need, indications, patient selection and pre-transplant medical care

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Adult liver transplantation in the United Kingdom (I): need, indications, patient selection and pre-transplant medical care

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Adult liver transplantation in the United Kingdom (I): need, indications, patient selection and pre-transplant medical care.

Abstract

Chronic or acute liver failure and primary liver cancers can be effectively managed with liver transplantation (LT). The range of indications for LT is increasing but there is a mismatch between the numbers of available donations and current needs. Specific criteria for the listing of patients exist but, at minimum, the predicted mortality without transplantation must exceed that with transplantation, coupled with a 50% predicted 5-year survival following LT. The risk posed by liver disease must be weighed against the risk of LT considering the patient's co-morbidities, age, nutritional status and behavioural factors in a complex assessment process. This review will focus on current UK practice in the selection and care of patients being assessed for liver transplantation.

Key Points and Key Words

Liver transplantation offers a significant survival benefit for appropriately selected patients

There is a current mismatch between suitable donor organs and patient needs

Strict national listing criteria for transplantation for acute and chronic liver disease aim to equitably target scarce resources to patients who will gain significant benefit

A broad range of factors including disease aetiology and severity, psychological, behavioural and social factors and nutrition must be considered when offering liver transplantation

Assessment of patients and care whilst awaiting transplantation is complex and requires multidisciplinary input.

Liver transplant, patient selection, indications, assessment, optimisation

Liver transplantation (LT) is a lifesaving intervention in acute and chronic liver disease. This article reviews the indications, selection process and pre-operative medical care for adult LT recipients in the UK.

LT is indicated in advanced chronic liver disease, fulminant (sub)acute liver failure and primary liver cancer. Advanced liver disease has a poor prognosis without transplantation: refractory ascites is associated with 50% mortality at 1 year (*Moreau et al 2004*) and decompensated liver disease has a median survival of 2 years and 25% survival at 5 years (*D'Amico et al 2006*). Survival for adults following LT in the UK is 92% at 1 year and 80% at 5 years for elective transplantation and 90% and 80% respectively for super-urgent LT (*Martin et al 2015*) and therefore offers patients a considerable survival benefit. However, despite the benefits of LT there is also considerable mortality and morbidity hence patient selection is crucial.

Increasing need and limited availability

LT numbers are rising but the need is increasing more rapidly: 882 LTs were performed in the year to 2015 between the seven UK centres, rising from fewer than 700 per annum in the mid 2000s. However, the number of patients waiting for LT in the UK more than doubled between 2008 and 2015 with over 500 adult patients currently on the waiting list (*Martin et al 2015*). The rise in LT numbers has been enabled by increasing use of livers from donors with cardiac death and a minimal increase in donations from donors with brain death. Due to the current shortage of suitable donor livers, 2 years after joining the list 20% of adult patients will have died or been removed from the waiting list and 4% will still be waiting for transplantation (*Martin et al 2015*).

Despite the relative scarcity of suitable donations the population requiring LT will continue to grow. Liver disease is increasing in prevalence (Williams et al 2014) and there are many patients who may benefit from LT who are not currently being assessed. A significant proportion of cirrhotic patients are never assessed for transplantation despite this being the treatment that has the potential to offer greatest benefit. Many unassessed patients are correctly not referred due to comorbidities or other absolute contraindications (CIs), however there is likely a significant unmet need for LT in the UK and the scarcity of donations is a major barrier to the transplant programme.

Indications for liver transplantation:

For LT to be in a patient's interests predicted survival following LT must exceed that without LT. Furthermore, under current UK guidance, patients should have a predicted 5 year survival of >50% to

ensure maximal utility for each liver transplanted and to avoid patients undergoing complex, major surgery with significant associated morbidity for lesser longer term benefit. Registration for LT therefore requires patients to meet minimum-listing criteria within four broad indications: acute liver failure (ALF), chronic liver disease, variant syndromes and primary liver cancer (see table 1).

Acute liver failure

ALF is a syndrome characterised by rapid onset of liver dysfunction with associated coagulopathy and encephalopathy. It carries a high risk of mortality and all patients with ALF should be discussed with a tertiary liver unit with transplantation facilities. There are specific and unique features to the clinical management of ALF (Whitehouse & Wendon, 2013) which should be delivered in an intensive care unit environment. The listing criteria differ for ALF due to paracetamol toxicity and non-paracetamol ALF are derived from the King's College Criteria (KCC) (*O'Grady et al, 1989*). However there are limitations to these criteria as some patients die from liver failure despite not meeting these criteria: the sensitivity and specificity of the KCC for mortality are 58% and 89% for paracetamol toxicity (*McPhail et al 2016*) and 68% and 82% for non-paracetamol liver failure (*McPhail et al 2010*) with a NPV of 47-92% (*Pauwels et al 1993, Anand et al 1997, Dhiman et al 2007, Simpson et al 2009*) suggesting that perhaps as few as half of patients who die from acute liver failure reach current listing criteria.

Elective transplantation

Chronic liver disease: progressive liver disease is associated with deteriorating hepatic synthetic function, renal function and sodium homeostasis. These parameters are modelled by the United Kingdom End-stage Liver Disease (UKELD) score (see box 1) which was developed from mortality data for patients listed for liver transplantation without hepatocellular carcinoma (HCC). A score of >49 predicts an annual mortality risk of 9% (*Barber et al 2011)* which exceeds the 1st year mortality risk of undergoing LT hence is used as a threshold for LT listing.

Despite the UKELD score's sensitivity for prediction of mortality, many patients with a qualifying UKELD score would not benefit from LT. For example patients with established chronic kidney disease may achieve a score >49 without intrinsic liver dysfunction. Hence patients with a qualifying UKELD are considered for LT only in a suitable clinical setting e.g. with attendant ascites or hepatic encephalopathy.

Variant syndromes: several clinical scenarios are associated with poor liver-related prognosis or poor quality of life and patients may gain benefit from LT independent of their UKELD score (see table 1). Common indications are diuretic resistant ascites, chronic hepatic encephalopathy (HE) and recurrent cholangitis. The risk-benefit balance of LT for quality of life indications must be carefully considered and patients counselled accordingly.

Hepatocellular carcinoma: LT has a key role in the management of HCC where resection is not possible. Various listing criteria meet acceptable mortality outcomes for LT in the setting of HCC and the UK uses a modified version of the Milan criteria (see table 1) (*Mazzaferro et al 1996*) which predict a low risk of relapse and death. Current UK outcomes for HCC managed by LT are 68.7% 5-year survival (*NHS Blood and Transplant 2014*) and HCC accounted for 25% of adult LT in the year to March 2014 (*Martin et al 2015*). Patients do not need to meet a minimum UKELD score but must have a predicted survival of at least 50% at 5 years with LT and not have adverse tumour biology. Downstaging HCC with radiofrequency ablation or transarterial (chemo)embolisation to meet criteria for transplantation is permitted.

Selection process

All patients with cirrhosis or acute liver failure should be considered for transplantation as currently it is the intervention that offers the greatest prognostic benefit. However patients with a high predicted risk of graft failure, perioperative death or limited 5 year survival are not offered LT. It is imperative that patients who may benefit from LT are referred for assessment early. Patients who have absolute CI and could not qualify for transplantation should not be referred. Those who are not suitable for LT should be considered for referral to palliative care services due to the poor prognosis and high symptom burden of advanced liver disease.

Typically patients referred for LT assessment will be seen by a transplant hepatologist and other members of the multidisciplinary team (MDT) for an assessment of their liver disease and comorbidities to determine a secure indication for LT and no contra-indications (table 2) and that patients are motivated for LT. Common barriers to transplantation can include cardiovascular fitness, poor nutritional state and behavioural, drug and alcohol disorders that may need to be assessed by specialists prior to further work up (see below).

Potential candidates undergo a comprehensive multidisciplinary assessment including hepatologists, transplant surgeons, specialist nurses in LT, anaesthetists, drug and alcohol services, nutritionists, psychologists and specialists from other clinical disciplines where indicated. The assessment typically occurs as an inpatient, which has several aims:

- Identify and optimise factors that may affect patient survival whilst on the waiting list e.g. oesophageal varices, viral hepatitis or ascites.
- Identify predictors of high operative or anaesthetic risk (see linked articles) e.g. cardiac dysfunction, pulmonary hypertension, pulmonary dysfunction and poor nutritional status.
- Screen for contraindications to LT.

- Allow patients to meet the members of the transplant team and become familiar with the transplant unit.
- Educate patients and their family about the transplantation process, postoperative and long term care.

There is a common set of assessments for most patients (table 3) and others will be tailored to individual patient's needs. Following assessment, each patient is discussed by the transplant MDT and if a patient meets listing criteria, will potentially gain benefit from LT and has no absolute contraindications they should be put forward for transplantation.

Patients with acute liver failure are listed on the national super urgent list. The selection process applies the same principles as for elective transplantation: a patient must meet minimum listing criteria as outlined in table 1, they should have a predicted 5 year survival of more than 50% with transplantation and no absolute contraindications.

Risk assessment

Drugs and alcohol: due to the link between alcohol and drug dependency and some forms of liver disease special consideration regarding these issues is required. A detailed drug and alcohol history must be obtained from all patients to inform the aetiology of liver disease, optimise chronic liver disease management due to synergistic liver injury, identify other related pathology (e.g. neuropathy, cardiomyopathy, occult sepsis), assess social and psychological support and risk factors and identify indicators for LT failure.

Where alcohol was a contributory factor to liver disease or there is a history of illicit drug use patients should be assessed by a substance misuse team. Active alcohol consumption following clinical recommendation of abstinence, coupled with a clear explanation to the patient the implications of continuing to drink against medical advice, is an absolute contraindication to LT. Abstinence may result in recompensation of liver disease to the point that LT is no longer required. There is no nationally stipulated minimum period of abstinence prior to consideration of transplantation in the UK, but 6 months abstinence is commonly requested if the patient is able to wait.

Drug use is linked with liver disease due to the high prevalence of viral hepatitis amongst injecting drug users. Patients on stable drug replacement and maintenance therapy can be considered for transplantation, but illicit drug use raises considerable concerns. The overriding principles with respect to drug and alcohol use relate to the potential for transplant failure. Drug and alcohol dependency raise the risk of drug seeking behaviour taking primacy over engagement with health care and concordance

with post LT treatment such as immunosuppression, represent a risk for recurrent liver disease and a potential for harms such as infection from injection practices in the setting of immunosuppression.

A substance misuse team will advise the transplant MDT of the predicted risk of recidivism and provide support and advice for patients regarding long-term strategies to support abstinence and address contributing psychological or psychiatric co-morbidities. Patients with a considerable risk of harm from ongoing illicit drug use or of a return to harmful alcohol consumption should not be offered LT.

Age and comorbidities: There are few absolute contraindications to LT (see table 2), however LT should only be offered if there is a 5-year predicted survival >50% with LT. Co-morbidities and age may have an additive effect on predicted mortality and these factors need to be considered holistically.

Age: there is no current upper age limit for transplantation in the UK. Some studies demonstrate that long-term survival decreases with age above 60 (Collins et al 2000, Malinis et al 2014) mainly due to malignancy and infection whereas others found no differences in outcomes for appropriately selected older recipients (Bromley et al 1994, Garcia et al 2001, Cross et al 2007, Sonny et al 2015).

Co-morbidities: common co-morbidities are screened for with particular attention to those associated with the aetiology of liver disease, including coronary artery disease, hypertension and type 2 diabetes in patients with NAFLD, autoimmune disease in those with immune-mediated liver diseases, inflammatory bowel disease and dysplasia in patients with primary sclerosing cholangitis, renal dysfunction in viral hepatitis and NAFLD. Co-morbidities should be optimally treated and their impact on projected survival following LT be considered cumulatively.

Malignancy: prior, treated extra-hepatic malignancy is not an absolute contraindication to LT, however the risk of recurrence in the setting of long-term immunosuppression needs to be considered for each patient with input from an oncologist tailored to that patient and tumour biology. European guidelines suggest a 5-year interval from treatment prior to LT would be suitable to exclude recurrence, but there is little evidence for this approach (*European Association for the Study of the Liver 2016*). Patients should undergo conventional screening for occult malignancy in line with national screening guidelines with a high index of suspicion for, for example, upper GI tract, pulmonary and ENT cancers, in patients with a history of alcohol or tobacco addiction. Active cancer, outside primary HCC, epithelioid haemangioendothelioma or hepatoblastoma and non-melanoma skin cancer is an absolute contraindication to LT.

Infections: screening for infection with hepatotropic viruses, HIV infection, herpes viruses and *Toxoplasma* is routine. Hepatitis B, C and HIV all have highly effective treatments that are tolerated in chronic liver disease and following transplantation and patients should be offered these when

appropriate. Other latent infections such as TB should be considered and screened for. Active extra-hepatic sepsis is a contraindication to liver transplantation and the evolution of interval sepsis, including spontaneous bacterial peritonitis, will require delay of LT until resolved.

Smoking: is not a contraindication to LT but patients are strongly encouraged to quit smoking as there is evidence of a raised risk of mortality (Leithead et al 2008), malignancy (Watt et al 2009), hepatic vascular complications (Pungpapong et al 2002), biliary complications (Mathur et al 2011) and an association with relapse to alcohol consumption (Rodrigue et al 2013).

Nutrition: the evidence for an impact of obesity on LT outcomes is mixed. Some studies demonstrate an increase in mortality (Nair et al 2002, Hilingsø et al 2005, Dick et al 2009) whereas others show no increase in mortality but more complications including longer length of stay post LT or post-operative infections (Hakeem et al 2013, Singhal et al 2015) and others demonstrate no increase in complications (Braunfeld et al 1996, Fujikawa et al 2006) with obesity or morbid obesity. However, any mortality risk associated with obesity appears lower than the risks of non-transplantation in patients with qualifying indications for LT and there is no national upper BMI limit for LT in the UK.

Malnutrition is common in advanced liver disease and low BMI has a negative impact on outcomes pre- and post-LT including survival and length of post-operative recovery (Dick et al 2009, Merli et al 2010, DiMartini et al 2013, Ferreira et al 2013, Ney et al 2015). Low BMI is a useful marker of prognosis but there remains little evidence of a survival benefit with nutritional interventions (Langer et al 2012) although nutritional indices, rate of recovery post LT and other clinical indices are improved with expert nutritional intervention (Ferriera et al 2010, Langer et al 2012).

Optimisation

Many chronic liver disorders and complications of liver disease have effective treatments and care is taken to optimise patient's clinical status whilst on the waiting list. This aims to reduce the risk of LT, improve long-term graft function and may lead to improvement to the point where LT is no longer required. Table 4 outlines the common diseases and complications of liver disease that should be treated prior to LT.

Care whilst on the list

Whilst a patient is waiting for transplantation they require regular clinical review and assessment to monitor their clinical status including screening for *de novo* HCC or progression of established HCC,

portal venous thrombosis, pulmonary hypertension and cardiac dysfunction. Progression of liver disease may prompt escalation of patient's position on the waiting list. Specialist support for the psychological stresses associated with waiting for LT will be available. Currently each transplant unit identifies their priority cases for transplantation based upon clinical liver disease severity and projected mortality. This is due to change with the implementation of a national organ allocation process.

Conclusions

LT offers a significant survival benefit for patients with ALF or chronic liver disease but demand is outstripping availability due to the limitations on organ availability and this is predicted to worsen as the prevalence of liver disease increases. Patient selection is critical to good patient outcomes and comprehensive multidisciplinary care is required to select and optimise patients for the transplant programme. Careful consideration of care for those for whom transplantation is not suitable is essential. In the following article we will discuss the medical management of patients post-liver transplantation.

Conflicts of interest:

The authors declare no conflicts of interest.

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UKELD: $[(5.395 \times \ln(\text{INR})) + (1.485 \times \ln(\text{creatinine})) + (3.13 \times \ln(\text{bilirubin})) - (81.565 \times \ln(\text{Na}))] + 435$

Box 1: United Kingdom End-stage Liver Disease score formula (Barber et al 2011)

Table

Transplant Category	Indication	Criteria
Super-urgent	Paracetamol toxicity	pH<7.25 after 24hrs following fluid resuscitation
		PT>100s/INR>6.5 AND Cr>300µmol/L or anuria AND ≥grade 3 HE
		Serum lactate >5mmol/L on admission or >4mmol/L after 24hrs fluid resuscitation AND HE
		2/3 of point 2 with deterioration
	Acute viral hepatitis / cocaine or ecstasy induced	PT>100s/INR>6.5 AND any grade of HE
		Any grade HE and 3 of: age >40, jaundice to HE time of >7 days, bilirubin >300µmol/L, PT>50s/INR>3.5
	Seronegative hepatitis / idiosyncratic DILI	PT>100s/INR>6.5
		INR>2 AND 2 of: age >40, jaundice to HE time of >7 days, bilirubin >300µmol/L, PT>50s/INR>3.5
	Acute Wilson's or Budd-Chiari syndrome	Coagulopathy and any grade of HE
	Post liver transplantation	
		Hepatic artery thrombosis <21 days post LT
		Early graft dysfunction
	Post total hepatectomy or living related donation	
Chronic liver disease	Alcoholic liver disease	
	NAFLD	
	Chronic viral hepatitis	
	Autoimmune liver diseases	
	Hereditary haemachromatosis	UKELD ≥49
	Wilson's disease	
	α-1 antitrypsin deficiency	
	Congenital hepatic fibrosis	

	(and others) 2□ sclerosing cholangitis	
Variant syndromes	Diuretic resistant ascites Chronic HE Intractable pruritus Hepatopulmonary syndrome FAP Familial hypercholesesterolaemia Polycystic liver disease Hepatic epithelioid haemangioendothelioma Sickle cell hepatopathy	TIPS can be considered as an alternative With ≥2 admission per year Due to cholestatic liver disease In the absence of chronic lung disease
Liver tumours	Hepatocellular carcinoma	Single lesion ≤5cm *or* Up to 5 lesions all ≤3cm *or* Single lesion ≤7cm with no evidence of progression or spread over 6 months No evidence of vascular invasion or distal spread

PT=prothrombin time, INR = international normalised ratio, Cr=serum creatinine, HE=hepatic encephalopathy, DILI=drug induced liver injury, NAFLD=non-alcoholic fatty liver disease, UKELD=United Kingdom End-stage Liver Disease score, TIPS=transjugular intrahepatic portosystemic shunt, FAP=familial amyloid polyneuropathy

Table 1: indications and minimum listing criteria for liver transplantation in the United Kingdom, adapted from POL195/4 (NHS Blood and Transplant 2015).

Contraindications to liver transplantation	
Absolute contraindications	Failure to meet criteria outlined in table 1
	Acute alcoholic hepatitis (outside of trial setting)
	More than 2 episodes of returning to alcohol use after advice to stop
	Drinking alcohol whilst on LT waiting list (ALD only)
	Ongoing illicit IV drug use
	Recurrent non-adherence to medical care
	Active disseminated malignancy
	Co-morbidities giving <50% predicted 5 year survival with LT
	Severe pulmonary hypertension (non-responsive to medical therapy)
Relative contraindications	Age >65
	Chronic source of infection
	Technical considerations (may include portal venous thrombosis, aberrant vascular or biliary anatomy)
	Poor nutritional state (under or overweight)
	Comorbidities including smoking

Table 2: Relative and absolute contraindications to liver transplantation

Typical investigations prior to liver transplantation	
General investigations	Full history and examination
	Bloods for cross match, full blood count, liver function, renal function, coagulation screen, alpha fetoprotein, HIV screen
	Liver aetiology screen
	Electrocardiogram
	Transthoracic echocardiogram with estimated pulmonary artery pressures
	Chest X ray
	Pulmonary function tests
	Arterial blood gas analysis
	Formal assessment of glomerular filtration rate
	Oesophagogastroduodenoscopy
	Computed tomography of liver (portal venous and arterial phase contrast)
	Cytomegalovirus and toxoplasma screening
	Urine protein:creatinine ratio
	Bone densitometry
Patient specific investigations	Psychology assessment
	Random blood alcohol and drugs of abuse screen
	Right sided cardiac catheter studies
	Coronary angiogram/myocardial perfusion scan
	Interferon gamma release assay
	Targeted cross sectional imaging
	Liver biopsy
	Colonoscopy
	Cancer screening tests (as per general population)

Table 3: Investigations required during workup for liver transplantation

	Optimisation strategy	**Goal**
Primary liver disease		
Alcoholic liver disease	Psychological and substance misuse services support	Prevent relapse to drinking Develop strategies to maintain sobriety
Autoimmune hepatitis	Glucocorticoids and immunomodulator therapy	Control active hepatitis
Hepatitis B	Nucleotide analogue therapy	Suppression of HBVaemia Recompensation
Hepatitis C	Direct acting antiviral drugs	Clearance of virus Prevent recurrence in graft
NAFLD	BP, diabetes and lipid control Reduce BMI	Reduce cardiac/anaesthetic risks Reduce surgical complexity
HCC	Loco-regional therapies	Prevent progression of HCC outside of LT criteria
Haemachromatosis	Venesection	Limit disease progression and prevent secondary complications
Wilson's Disease	Chelation therapy	Limit disease progression
Primary Biliary Cholangitis	Ursodeoxycholic acid	Optimal disease control
Primary Sclerosing Cholangitis	Stenting of dominant strictures	Minimise risk of cholangitis and obstructive jaundice
Thrombotic diseases	Anticoagulation	Prevent clot extension or *de novo* thrombosis

Complications of chronic liver disease		
Hepatocellular carcinoma	6 monthly ultrasound scan, MRI liver or triple phase CT Consider alpha fetoprotein monitoring	Early identification of HCC
Ascites	Optimise diuretic regimen Consider TIPS	Reduce risk of spontaneous bacterial peritonitis Improve nutrition (calorific cost of ascites and distension) Improve mobility/functional reserve
Varices	Beta-blockade Variceal band ligation	Avoid haemorrhage and subsequent decompensation
Malnutrition	Specialist assessment Nutritional supplements NG/NJ feeding	Improve mobility/functional reserve Reduce anaesthetic risk Improve wound healing
Hepatic encephalopathy	Laxatives Rifaximin	Improve mobility/functional reserve and quality of life

Table 4: Medical strategies to optimise clinical status for patients whilst on the waiting list