Guidelines for Referral for Liver Transplant Assessment

March 2012

Summary of Recommendations

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Indications for Referral for Liver Transplantation Assessment

Acute and sub-acute liver failure

Paracetamol hepatotoxicity

Patients with paracetamol (acetaminophen) hepatotoxicity should be discussed with a transplant unit if they have any of the following in the context of coagulopathy (IIa):

a. Evidence of any renal impairment or hepatic encephalopathy
b. pH < 7.4 at any time after ingestion.
c. Elevated serum lactate >2.5 mmol/l after fluid resuscitation.

Particular caution should be taken in cases associated with paracetamol ingestion staggered over time, malnutrition, anticonvulsant drug use or a history of prior excess alcohol consumption.

Stabilisation of patients prior to transfer must be discussed with the transplant unit (IIa).

Non-paracetamol-induced acute liver failure

In all cases the development of any grade of encephalopathy should prompt discussion with a transplant unit (IIa).

In all cases a coagulopathy with INR > 1.5 or serum creatinine > 150 mmol/l should prompt discussion with a transplant unit (IIa).

In all cases the presence of any additional organ failure should prompt discussion with a transplant unit (IIa).

Patients who are encephalopathic or have ascites in the context of an acute presentation of auto-immune hepatitis, should be discussed with a liver transplant unit (I-C).

Patients with acute liver failure secondary to Wilson's disease should be referred for liver transplantation immediately (I-B).

Patients diagnosed with acute Budd-Chiari displaying signs of hepatic decompensation or coagulopathy should be discussed with a Transplant Unit.

Sub-acute or late-onset hepatic failure

Patients with sub-acute or late-onset hepatic failure should be discussed with a transplant unit at the stage of recognition of the condition (IIb).

Indications for referral for Elective Liver Transplantation Assessment

Primary Liver Cancer

Patients with cirrhosis who are otherwise appropriate candidates for a liver transplant and are found to have liver lesion(s) characteristic of HCC within liver transplant criteria should be referred to a Liver Transplant Unit (I-A).

Criteria for listing for liver transplantation;
a single lesion ≤ 5cm diameter
up to 5 lesions all ≤ 3cm diameter
a single lesion > 5cm ≤ 7cm diameter where there has been no evidence of tumour progression (volume increase by <20%), no extrahepatic spread, no new nodule formation) over a 6 month period. Locoregional therapy +/- chemotherapy may be given during that time.

Chronic Liver Disease

Generic recommendations on referral to a liver transplant unit

Patients with chronic liver disease and a UKELD >49 should be referred for consideration of liver transplantation unless contra-indications exist.

Patients developing decompensated cirrhosis (ascites or hepatic encephalopathy) should be discussed with a liver transplant unit (IIa).

Physicians involved in the care of patients with cirrhosis should inform patients of the need to improve all potentially modifiable risk factors that impact on long-term survival and fitness for liver transplantation.

Patients with cirrhosis who develop diuretic-refractory or diuretic-intolerant ascites should be rapidly referred for consideration of liver transplantation (I-A).

Patients with chronic hepatic encephalopathy or repeated admissions due to recurrent hepatic encephalopathy that is refractory to optimal medical management should be referred for consideration of LT (I-C).

Patients with hepatopulmonary syndrome should be referred for consideration of liver transplantation (I-C).

Patients who are found to have porto-pulmonary hypertension should be discussed with a liver transplant unit regarding suitability for the procedure (II-C).

Liver transplantation is currently contra-indicated in patients found to have severe porto-pulmonary hypertension (MPAP ≥45mmHg). Such patients should nevertheless be discussed with a liver transplant unit and in parallel with referral to a specialist in pulmonary hypertension in order that attempts to treat the PPH are commenced (II-C).

Disease-specific recommendations

Alcoholic liver disease

There are currently no disease-specific indications for liver transplantation in patients with alcohol-related liver disease. Indications for referral for consideration of liver transplantation in patients with alcohol-related cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Patients with non-resolving decompensated ALD should be discussed with a liver transplant unit.

Patients who are found to have hepatocellular carcinoma within transplant criteria at the point of initial diagnosis of ALD (even in the context of recent alcohol consumption) should be referred to the relevant liver transplant unit specialist MDT (II-C).

The following issues indicate patients with ALD that are not appropriate referrals for liver transplantation:
- recurrent decompensated ALD in the context of ongoing or recurrent alcohol consumption are not appropriate referrals for liver transplantation.
- prior refusal to engage with alcohol-support/substance misuse services.
- significant other alcohol-related end-organ damage, including dementia or cardiomyopathy.

Nonalcoholic steatohepatitis- (NASH) related cirrhosis

There are currently no disease-specific indications for referral for liver transplantation in patients with NASH-related cirrhosis. Indications for referral for consideration of liver transplantation in patients with NASH-related cirrhosis should be in line with agreed criteria for chronic liver disease and/or hepatocellular carcinoma (I-C).

Hepatitis C-related cirrhosis

There are currently no disease-specific indications for referral for liver transplantation in patients with HCV-related cirrhosis. Indications for referral for consideration of liver transplantation in patients with HCV-related cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Hepatitis B-related cirrhosis

There are currently no disease-specific indications for referral for liver transplantation in patients with HBV-related cirrhosis. Indications for referral for consideration of liver transplantation in patients with HBV-related cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

HIV with HBV and/or HCV co-infection

There are currently no disease-specific indications for referral for liver transplantation in such patients. Indications for referral for consideration of liver transplantation in patients with HIV and cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Autoimmune Hepatitis

There are currently no disease-specific indications for referral for liver transplantation in patients with cirrhosis secondary to auto-immune hepatitis. Indications for referral for consideration of liver transplantation in patients with auto-immune chronic active liver disease should be in line with agreed criteria for chronic liver disease (I-C).

In patients with liver failure, bridging necrosis on biopsy or in jaundiced patients whose MELD score does not rapidly improve on treatment, contact should be made with a liver transplant centre (I-B).

Patients who are encephalopathic or have ascites in the context of an acute presentation of auto-immune hepatitis, should be urgently discussed with a liver transplant unit (I-C).

Primary Biliary Cirrhosis

There are currently no disease-specific indications for referral for liver transplantation in patients with primary biliary cirrhosis. Indications for referral for consideration of liver transplantation in patients with primary biliary cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Primary Sclerosing Cholangitis

Indications for referral for consideration of liver transplantation in patients with primary sclerosing cholangitis should be in line with agreed criteria for chronic liver disease (I-C).

In addition, the presence of recurrent, refractory bacterial cholangitis in a patient with extensive PSC is also an indication for referral to a liver transplant unit (I-C).

Liver transplantation is contra-indicated in patients with PSC who have superimposed cholangiocarcinoma (II-C).

Because of the high incidence of colon cancer, regularly scheduled colonoscopies should be performed both before and after transplantation in all patients who have inflammatory bowel disease (II-C).

Haemochromatosis

There are currently no disease-specific indications for referral for liver transplantation in patients with cirrhosis secondary to haemochromatosis.

Consideration should be given to the diabetic status and possible cardiac involvement in patients with haemochromatosis (I-C).
Consideration should be given to de-ironing patients with haemochromatosis referred for LT (IIa-C).

Alpa1-antitrypsin-related liver disease

There are currently no disease-specific indications for referral for liver transplantation in patients with cirrhosis secondary to alpha1-antitrypsin accumulation. Indications for referral for consideration of liver transplantation in patients with cirrhosis secondary to alpha1-antitrypsin accumulation should be in line with agreed criteria for chronic liver disease(I-C).

Patients require detailed lung function assessment prior to transplant and must be told to stop smoking (I-C).

Cystic Fibrosis

Patients with cystic fibrosis–associated liver disease should be referred early for liver transplantation if there are signs of deterioration of liver function or evidence of significant portal hypertension (I-C).

Wilson's Disease

Patients with decompensated cirrhosis not responding to chelation treatment should be referred for liver transplantation (I-B).

Patients with acute liver failure due to Wilson's disease should be referred for liver transplantation immediately (I-B).

Polycystic liver disease

Patients with polycystic liver disease who have massive hepatomegaly resulting in abdominal pain with poor quality of life should be referred for consideration of liver transplantation. For those patients who have associated renal dysfunction, simultaneous liver-kidney transplantation may be considered (I-C).

Porphyrias

For patients with EPP, referral for consideration of LT should be made if there is evidence of jaundice.
Criteria for referral for liver transplantation in acute intermittent porphyria or variegate porphyria are either recurrent refractory attacks of porphyria or a severe attack with neurological deficit despite medical therapy (I-C).

Oxalosis

Patients with primary hyperoxaluria with who have evidence of progressive renal impairment should be discussed with a liver transplant unit at an early stage (I-C).

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Glycogen storage disease

Patients with glycogen storage disease whose symptoms are not controlled by optimal medical management or who are found on imaging to have developed hepatic adenoma(s) should be referred to a liver transplant unit (IIa-C).

Exceptional circumstances

Beyond these recommendations, there are further, clinically very rare, situations in which liver transplantation may be considered. These include other metabolic liver disease in specific settings (some patients with Gaucher's disease), as well as epithelioid haemangioendothelioma and, in extreme settings, hereditary haemorrhagic telangectasia with severe hepatic involvement or giant cavernous haemangioma. If it is not clear whether liver transplantation would be considered in exceptional circumstances, discussion with a liver transplant unit is recommended.

1 Background

1.1 Introduction

1.1.1 There are a number of reasons why there is a need for clear guidelines describing the timing of referral of patients to liver transplant units for both acute and chronic liver disease. Firstly, timely referral allows the transplant unit the required period to assess the patient fully and gives the potential candidate time to review all clinical options and make their decisions in timely fashion without pressure. Secondly, late referral jeopardises post transplant outcomes as pre-transplant status is one factor dictating post transplant hospital stay and mortality[1]. Thirdly, clear national guidance to referring hospital as to which candidates are eligible for transplantation will minimise disparities in access to this important health resource. The degree to which the current differences in geographic prevalence of liver transplantation reflects differences in disease prevalence or differences in referral for liver transplantation remains unclear. Now that national selection criteria for the transplant list have been introduced it cannot be because such criteria differ between units.

1.1.2 A National Liver Disease Strategy is currently being drawn up, driven by the increasing prevalence of liver disease and mortality from end-stage liver disease in the United Kingdom. It is likely that strategy will want to clarify the overall tiers or strata of Hepatology care available to patients, ranging from Primary Care through to the nationally designated Liver Transplant Units. It is also likely that the strategy will wish to promote the need for clarity concerning the transition points and guidelines for referral from one tier to the next. It is hoped that this document will further that goal.

1.1.3 The importance of early discussion of cases with a transplant unit is crucial, even if it does not result in a transfer of care. This can allow early discussion concerning alternative treatment modalities to prevent further deterioration as well as the timely planning of any transfer should that be necessary. In defining criteria for referral for transplantation it is accepted that erring on the side of caution with early referral even at the expense of some increase in ultimately unnecessary transfers may be the better management algorithm.

1.1.4 There are few studies that have specifically examined the necessary timing of transfer to transplant units and therefore the evidence base for many of these recommendations is low. The following grading system will be used:

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Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

1.2 Aims of transplantation

A number of aims of transplantation have been identified:

1.2.1 Maximise total patient and graft survival when judged from the point of registration for a transplant.
1.2.2 Minimise disparities in consistently measured waiting times until an offer of an organ for transplantation is made among patients with similar or comparable risk of death, medical and demographic characteristics or in relation to geography.
1.2.3 Maximise the availability of transplantable organs by promoting consent to donation, procurement efficiency, splitting of grafts where appropriate, and reduce the number of discarded organs.
1.2.4 Provide a balance between improvement in the quality and quantity of life
1.2.5 Avoid transplantation with a 5 year survival less than 50%
1.2.6 Provide transparency as to the allocation process.

1.3 Current selection criteria for Liver Transplantation

1.3.1 Super-urgent liver transplant waiting list criteria (Box 1)

Box 1; Selection criteria for Super-urgent liver transplantation.

	Acetaminophen (Paracetamol) hepatotoxicity
1	pH <7.25 > 24 hours after overdose and after fluid resuscitation
2	Serum lactate > 3.5 mmol/l > 24 hours after overdose on admission or >3.0 mmol/l after fluid resuscitation
3	PT >100 seconds (INR >6.5) + creatinine >300 µmol/l anuria, + grade 3-4 encephalopathy
4	Two criteria from above plus evidence of clinical deterioration (increased ICP, FiO2 >50%, increasing inotrope requirements) in the absence of clinical sepsis
	Other aetiologies
5	Seronegative hepatitis, hepatitis A, hepatitis B, drug-induced liver failure INR > 6.5 or PT >100 seconds
6	Seronegative hepatitis, hepatitis A, hepatitis B, drug-induced liver failure. Any 3 from; unfavourable aetiology; age> 40yr; J-E>7 days; bilirubin > 300 mmol/l; INR > 3.5
7	Aetiology: Acute presentation of Wilson's disease, or Budd-Chiari syndrome. A combination of coagulopathy, and any grade of encephalopathy
8	Hepatic artery thrombosis on days 0 to 21 after liver transplantation
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/l, absence of bile production
10	The total absence of liver function (e.g. after total hepatectomy)
11	Any patient who has been a live liver donor (NHS entitled) who develops severe liver failure within 4 weeks of the donor operation

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1.3.2 Elective Liver Transplant waiting list criteria (Box 2)

1.3.2.1 Chronic liver disease

Patients can be considered for elective transplantation if they have an anticipated length of life or survival at one year, as judged by a UKELD score (Barber 2011) 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 only 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.

1.3.2.2 Hepatocellular carcinoma

Current criteria were introduced in July 2008. It is likely that there will be further modification to these in future in order to better assess tumour biology and predict those patients who are most likely to benefit from a transplant with an acceptably low recurrence rate.

1.3.2.3 Variant syndromes

A number of syndromes have been accepted where UKELD may not adequately reflect the risk of mortality on a transplant list or where transplantation is undertaken to alleviate symptoms and to improve quality of life.

1.3.2.4 Appeals Panel

If a centre wishes to register an adult (17 years or older) 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 is made in writing to members of the National Appeals Panel. The Appeals Panel is constituted of one physician or Surgeon from each of the three Regions; North (Leeds, Newcastle, and Edinburgh Liver Transplant Units); Central (Birmingham, and Cambridge Liver Transplant Units); Southern (Royal Free and King's Liver Transplant Units). To be selected decisions have to be unanimous.

Box 2; Selection criteria for elective liver transplantation.

Selection Criteria For Elective Transplantation
To be registered on the elective liver scheme, adult (17 years or older) patients awaiting a first elective liver transplant must meet one of the following three set criteria.

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).

2) Hepatocellular cancer (HCC)
Size assessed by the widest dimensions on either MDCT and MRI scan. A tumour (for the purposes of counting numbers) identified as an arterialised focal abnormality with portal phase washout.. Other lesions are considered indeterminate and do not count. Tumour rupture and an AFP >10,000 iu/ml are absolute contra-indications to transplantation, as are extrahepatic spread and macroscopic vascular invasion. The following are criteria for listing
• a single tumour ≤ 5cms diameter or
• up to 5 tumours all ≤ 3cms or
• single tumour >5cms and ≤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 waiting list place may be considered from the time of their first staging scan.

3) Variant syndromes
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 cholestastic 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) Hepatic haemangioendothelioma - Histological confirmation; not a single lesion amenable to resection; extra-hepatic spread confined to abdominal lymph nodes; minimum observation period of three months

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1.4 Contra-indications to liver transplant

As liver transplantation (LT) has become an accepted treatment modality for many complications of advanced liver disease, there has been a continued attempt to push the envelope to encompass new indications. Whilst in many instances this has resulted in good outcomes, this has also informed clinicians as to where the limits may lie in which patients currently have a predictably poor post-transplant outcome. With advances in understanding and of clinical management, these limitations to success of a procedure evolve, and this has been the case for liver transplantation. Issus such as active, uncontrolled HBV or HIV were previously regarded as contra-indications to LT and are not currently so. Portal vein thrombosis and morbid obesity have also in the past been regarded as such by virtue of high surgical risk, but are often now, in themselves, not considered to prohibit LT. In addition to gaining information about which liver conditions have a good outcome after LT and which do not, there has in parallel been a development in understanding of other factors pertaining to the recipient and to characteristics of the donor organ. As such, in evaluating each potential liver transplant recipient, consideration is made not only of the type and stage of liver disease and its complications, but all other recipient factors relevant to short-term and long-term survival after LT.

Older age, in itself, has previously been considered a contra-indication to listing for LT. Current data suggest that in Europe 20% of patients now undergoing LT are over 60 years old (www.eltr.org). European liver transplant registry data does show a worse 3- and 12-month patient survival in this age group (Burroughs 2006), although other studies have found equivalent 5-year survival for selected recipients over the age of 65 in comparison to groups of recipients aged over 60 and also adult recipients less than 60 years of age (Cross 2007). Examination of historical data looking at predictors of outcome after LT in individuals over the age of 60, however, has found that, in addition to in-patient status (and in particular mechanical ventilation), recipient diabetes, serum creatinine, and hepatitis C seropositivity independently predict a worse outcome (Aloia 2010). As a consequence, age in combination with co-morbidities can predict a poor post-transplant outcome and therefore can preclude listing for a liver transplant.

With the increasing prevalence of obesity and the fact that this is an aetiological factor or co-factor in development of advanced liver disease, there has been more attention directed towards the surgical fitness of the morbidly obese for LT. Reported long-term outcomes published from the US on liver transplants undertaken in the 1990s have shown that such patients have a 57% 5-year mortality (Nair 2002) and this led to a BMI greater than 40 being recommended as a contra-indication to LT in the AASLD Guidelines of 2005. Subsequent analyses have come to differing conclusions (Pelletier 2007, Dick 2009). Currently, however, whilst it is recognised that morbid obesity is associated with a higher short-term morbidity, the long-term mortality rates of patients transplanted with a BMI >40 do not preclude LT. Importantly, however, it is clear that BMIs at the other extreme are associated with a marked increase in short-term mortality after LT (Dawwas 2008A, Dick 2009).

Another specific factor that has been found to be an independent predictor of a worse outcome after LT is an established diagnosis of diabetes (Pageaux 2009), particularly if requiring insulin. As with other co-morbidities, the presence of diabetes, whilst being recognised as an additional risk factor negatively impacting on long-term outcome, does not definitively predict a poor enough outcome to decline listing for LT. In the context of other co-factors, however, such as age (Aloia 2010), impaired renal function (Fabrizi 2011), cardiac disease (Plotkin 1996, Bilbao 2008) and evidence of other significant end-organ damage from DM, these can point to a poor long-term survival, such that listing for a liver transplant would not be recommended.

There is an increasing body of literature on cardiovascular assessment for fitness for LT and, when considering fitness for LT there are two aspects that are relevant. The first, and perhaps more easy to assess, is that of coronary artery disease (CAD) as it pertains to peri-operative risk. From this point of view, multi-vessel CAD has recently been reported to predict a significantly worse 1-year outcome post-LT (Yong 2010). The second issue is incorporation of coronary artery disease or cardiac functional deficits into prediction of medium- and long-term post-transplant outcomes. The means of assessing CAD and cardiac function in potential LT candidates are matters of continuing debate and are outwith the remit of his guideline, although both may need to be evaluated in higher-risk potential recipients. It is important that clinicians involved in the care of patients with chronic liver disease who may reach the point of consideration of LT are aware of the relevance of CAD and cardiac functional reserve. These issues need to be highlighted in any discussion with the relevant transplant unit and patients need to be made of aware that these issues can preclude LT, even if otherwise indicated.

Substance Misuse

National Guidelines have been produced in relation to illicit drug use in potential liver transplant recipients (Liver Advisory Group 2007). These indicate that issues including current ongoing intravenous use of illicit or non-prescribed substances, non-compliance with treatment or failure to comply with assessment constitute contra-indications to listing for LT. Patience with ongoing dependency (eg opiates, benzodiazepines) should be given access to a substance misuse treatment programme.

Recommendations
Ongoing illicit drug use is considered as a contra-indication to liver transplantation (II-C).
Ongoing alcohol misuse despite previous advice from a healthcare professional to be abstinent is considered as a contra-indication to liver transplantation (I-C).
Patients seen with chronic liver disease using illicit drugs or abusing alcohol should be advised that ongoing substance misuse will preclude liver transplantation should this be required in the future. Where appropriate, referral to the local Substance Misuse Service should be made.

Malignancy

As emphasised above one of the major considerations in fitness for listing for LT is the issue of predicted long-term survival after the procedure. Hence pre-existing extra-hepatic conditions that impart a limited prognosis are considered to contra-indicate LT. In this context a recent history of malignant disease can often preclude LT, though the nature and stage of tumour and predicted prognosis is taken into account. The required duration between tumour diagnosis and transplantation is not known, though as would be expected a longer duration (greater than 5 years) as well as nature of original tumour are variables that impact recurrence rate (Penn 1997). One of the recognised long-term complications of liver transplantation is the increased rate of malignancy (Fung 2001, Chak 2010). What is not well established for most tumours is the impact of subsequent immunosuppression on a previously treated tumour, though it is anticipated that it may facilitate a higher rate of recurrence/progression.

Recommendation
Current malignancy is a contra-indication to liver transplantation.
It is recommended that staging and prognostic information regarding any history of malignancy is provided in the initial discussion with a liver transplant unit in order to clarify whether consideration of liver transplantation can be pursued.

Cholangiocarcinoma, (CC) seen in the context of chronic liver disease usually in PSC has a poor outcome after LT (Pinson 2003, Alvaro 2010, Gu 2011) and as a result is currently regarded as a contra-indication to LT. It is well recognised that making the diagnosis of CC on the background of PSC can be very challenging and early involvement of a specialist MDT at an early stage is recommended to establish or exclude the diagnosis. This assessment should follow a cancer pathway and if there is uncertainty about the presence or absence of superimposed CC in a patient with advanced PSC, discussion with a liver transplant unit is recommended.

Recommendation
The presence of cholangiocarcinoma in a patient with primary sclerosing cholangitis currently represents a contra-indication to liver transplantation (II-C).

Summary of Contra-indications to liver transplantation

The factors that contra-indicate liver transplantation are those that predict high peri-operative mortality or a 5-year survival probability of less than 50%.

Current malignancy is a contra-indication to liver transplantation (III-C).
Previous history of malignancy with significant recurrence risk can contra-indicate liver transplantation.

The presence of cholangiocarcinoma in a patient with primary sclerosing cholangitis currently represents a contra-indication to liver transplantation (II-C).

Poor cardiac function or advanced coronary artery disease is a contra-indication to liver transplantation (III-C).

Symptomatic peripheral vascular disease is associated with poor 5-year survival and is a contra-indication to liver transplantation (III-C).

Factors that are known to predict a worse outcome after liver transplantation, including renal disease, diabetes (particularly with diabetic complications) and poor nutritional status can contra-indicate liver transplantation (III-C).

Extremes of body mass index are associated with higher transplant risk and can contra-indicate liver transplantation (II-B).

Issues such as extensive porto-mesenteric venous thrombosis or prior extensive abdominal surgical history can preclude liver transplantation (II-B).

Significant lung disease can contra-indicate liver transplantation (III-C).

Advanced age, itself, is not a contra-indication to liver transplantation. Advanced age, however, is associated with an increased risk of co-morbid factors which impact negatively on transplant outcome, and evidence of co-morbidites in more elderly recipients does preclude liver transplantation (III-C).

Ongoing illicit drug use is considered as a contra-indication to liver transplantation(II-C).

Ongoing alcohol misuse despite previous advice from a healthcare professional to be abstinent is considered as a contra-indication to liver transplantation(I-C).

Patients seen with chronic liver disease using illicit drugs or abusing alcohol should be advised that ongoing substance misuse will preclude liver transplantation should this be required in the future. Where appropriate, referral to the local Substance Misuse Service should be made.

1.5 End-of-Life care planning

Referral for consideration of transplantation represents a very significant step in the management of any patient with liver disease and not all patients will be fit enough to be placed on the waiting-list for liver transplantation. Furthermore, even if listed, a patient may not necessarily receive a suitable donor organ, as currently the liver transplant waiting list mortality nationally is around 18%. It may therefore be appropriate that during the process of referral and subsequent assessment the referring clinician formally consider end-of-life care planning.

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2. Referral guidance - Acute Liver Failure

2.1 Paracetamol hepatotoxicity

The importance of early referral in cases with paracetamol-induced hepatotoxicity cannot be over-emphasised. Early discussion with a Liver Transplant Unit will allow facilitate timely transfer of patients who do need to come to a Transplant Unit, avoid unnecessary transfer of patients who will not come near to meeting super-urgent transplantation and also expedite diagnostic evaluation and assessment by the transplant team in order to maximise the possibility of a successful transplant. A further important aspect is that early discussion with a Transplant Unit can ensure optimal management of the hepatotoxicity and related problems (either in the Transplant Unit or in the local hospital) to minimise the likelihood of detrimental clinical sequelae. In those cases that require transplantation, prognosis is better in those transplanted earlier with lower grades of encephalopathy, emphasising the importance of early transfer.

A number of factors predictive of poor prognosis are relevant when considering referral in individual cases. The King's College criteria (O'Grady 1989) continue to demonstrate high specificity for mortality (94.6% (95% confidence interval 93-95.9%)) in meta-analyses (Craig 2010) although with a lower sensitivity. Elevated serum lactate is also a marker of poor prognosis (Bernal 2002, Schmidt 2006), but again has lower sensitivity. Later markers of poor prognosis include renal impairment and hepatic encephalopathy.

Age has previously been associated with a poor prognosis (Ostapowicz 2002) but a more recent cohort has not confirmed this (Schiodt 2009). In contrast other clinical contexts are associated with poor outcomes including malnutrition (Claridge 2010), a staggered overdose, and prior alcohol use (Simpson 2009, Lauterberg 1988).

Recommendations

Patients with paracetamol (acetaminophen) hepatotoxicity should be discussed with a transplant unit if they have any of the following in the context of coagulopathy (IIa):

a. *Evidence of any renal impairment or hepatic encephalopathy*
b. *pH < 7.4 at any time after ingestion.*
c. *Elevated serum lactate >2.5 mmol/l after fluid resuscitation.*

Particular caution should be taken in cases associated with ingestion staggered over time, malnutrition, anticonvulsant drug use or a history of prior excess alcohol consumption.

Stabilisation of patients prior to transfer must be discussed with the transplant unit (IIa).

2.2 Non-paracetamol-induced acute liver failure

Acute liver failure (ALF) of non-paracetamol aetiology often follows a very different clinical course to that resulting from paracetamol hepatotoxicity. Analysis of the data from King's demonstrates that the prognosis declines as the degree of liver dysfunction (as judged by Bilirubin) rises (Bernal, personal communication). Specifically the presence of hepatic encephalopathy in this group is associated with markedly worse survival (Bernal – manuscript in preparation). Furthermore, the King's observational data has demonstrated that additional organ failure is linked to a worse non-transplant outcome (Bernal – manuscript in preparation). A meta-analysis of published studies has found that the King's College criteria for non-paracetamol-induced ALF show good specificity, though more limited sensitivity (McPhail 2010).

Two additional issues are important to take into account. Firstly, that close monitoring of the evolution of liver function/organ failure is essential and much more informative in terms of prognosis than a single 'snapshot'. Secondly, consideration of the context of the patient is important in deciding about discussion with, or transfer to, a transplant unit. If the patient is in effect several hours away from a unit where they can be adequately monitored, then early advice from a transplant unit may be helpful.

Recommendations – non-paracetamol-induced ALF

In all cases the development of any grade of encephalopathy should prompt discussion with a transplant unit (IIa).
In all cases a coagulopathy with INR > 1.5 or serum creatinine > 150 mmol/l should prompt discussion with a transplant unit (IIa).
In all cases the presence of any additional organ failure should prompt discussion with a transplant unit (IIa).

2.3 Sub-acute/late onset hepatic failure

A less common, though recognised clinical sub-group are those patients who demonstrate evidence of sub-acute hepatic failure. This clinical sub-group is a heterogeneous group with varying aetiologies of liver disease including auto-immune, viral, drug-induced, Wilson's disease, Budd-Chiari and idiopathic. It was previously recognised within the King's criteria for listing for liver transplantation (O'Grady 1989) through inclusion of "jaundice to encephalopathy of > 7 days".

Establishing clear evidence-based indications for referral to a transplant unit is difficult in this clinical sub-group. It is recognised that the development of hepatic encephalopathy in this context predicts a worse outcome, but that early recognition of this condition is key and such cases should ideally be discussed with a transplant unit before encephalopathy develops.

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In addition to allowing timely listing for LT, this may facilitate early intervention to allow recovery of liver function without the need for transplantation,

Recommendations

Patients with sub-acute or late-onset hepatic failure should be discussed with a transplant unit at the stage of recognition of the condition (IIb).

Patients with sub-acute liver failure developing any degree of hepatic encephalopathy should be discussed urgently with a transplant unit (IIa).

3. Referral guidance – Primary Liver Cancer

In western societies around 95% of Hepatocellular carcinoma (HCC) develops in the context of cirrhosis. Although resection can be used for many patients with non-cirrhotic HCC, dependent on stage and location of disease, in patients with cirrhosis, resection can only be considered for the minority of individuals with a normal serum bilirubin and with a measured hepatic venous pressure gradient (HVPG) <10mmHg (Bruix 1996 and Llovet 1999). Long-term survival figures for such appropriately selected patients undergoing resection for HCC in the context of cirrhosis can exceed 70% at 5 years (Llovet 1999 and Huo 2007). Initial experience of LT for HCC with cirrhosis was poor, related to inappropriate patient selection, but subsequent literature has defined better the stage of tumour disease that can result in good patient and disease-free survival figures at 5 years. Patients within defined criteria based on the size and number of tumour(s) had 5-year survival rates of over 70% (Mazzaferro 1996). These criteria, known as the Milan or Mazzaferro criteria, have become established internationally as defining patients who were appropriate for acceptance on to liver transplant waiting lists on the basis of anticipated good post-transplant outcomes. Building on these criteria, various attempts have been made to better refine HCC criteria for LT given that some patients with HCC outside Milan criteria can have a good post-LT outcome and some patients with a single small HCC have a poor outcome after LT due to early and aggressive tumour recurrence. The outcomes of patients transplanted with extended criteria HCC have generally worse outcomes than the more restrictive Milan criteria with around 50% 5-year survival (Pomfret 2010). It is recognised that any extension to LT criteria for HCC will result in reduction of transplant benefit (Mazzaferro 2009 and Pelletier 2009), an issue that is difficult to reconcile with an ever-increasing mortality rate for those patients currently on the waiting list for LT (NHSBT). For patients listed for LT with or for HCC, the increasing median waiting times result in a higher likelihood of tumour progression and consequent removal from the LT waiting list. Data from the US suggest that here is an approximately 25% rate of drop-out from the transplant waiting list at 1 year (Yao 2002 and Freeman 2006).

There are ongoing efforts to improve determination of those individuals who would obtain the most benefit from liver transplantation. Size and number of HCC radiologically has some accuracy in predicting outcome as it is considered to be a surrogate of tumour stage (Hsu 1988, Shah 2007). A single snapshot image of tumour bulk and number does not, however, inform on tumour biology. Histological characteristics of the tumour including poor differentiation status and the presence of macro-or micro-vascular invasion have repeatedly been found to be independent predictors of post-transplant outcome (Jonas 2001 and Plessier 2004). Clearly this information is generally available after the event (*ie* on examination of the explanted liver). Biopsy of the tumour has been proposed as a means of getting information on differentiation status and the presence or absence of microvascular invasion before a decision about LT is made.

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The utility of targeted liver biopsy in this context is limited, however, by the lack of representivity of the sample obtained. It is known that HCC are frequently heterogeneous in their differentiation status even within a single tumour, and that microvascular invasion may often only be seen in a very small section of the HCC.

After a Consensus meeting of the UK Liver Transplant Units in 2008, incorporating the Milan criteria, but also evidence from the SRNR (Yao 2008 and www.hcc-olt-metroticket.org/) and an acceptance of the varying biology of HCCs, some relaxation of the Milan criteria was allowed, and these constitute the current HCC criteria for placement in the UK liver transplant waiting list (Box 2). These incorporated some elements that were felt to reflect tumour biology (rate of growth of larger tumours and markedly elevated serum AFP) As before, patients with extensive (large volume) disease, multifocal HCC and diffuse, invasive HCC as well as with macrovascular invasion or metastatic disease have a worse outcome and should not be considered for LT (AASLD Guidelines 2010 – www.aasld.org/practiceguideline and International Consensus Conference Report, Clavien 2012).

In view of the very good long-term disease-free survival figures for carefully selected patients with HCC in the context of cirrhosis, this treatment option needs to be considered alongside alternative treatment options such as, in particular, resection and radiofrequency ablation. Consideration of the appropriate treatment option for each patient will incorporate such factors as co-morbidities and stage of background liver disease as well as location of tumour(s). As such, patients picked up as having a focal liver lesion with the characteristics of HCC and within criteria for LT should be referred to a Liver Transplant Unit Tumour SMDT in order that, where appropriate, LT is considered.

Recommendation

Patients with cirrhosis who are otherwise appropriate candidates for a liver transplant and are found to have liver lesion(s) characteristic of HCC within liver transplant criteria should be referred to a Liver Transplant Unit (I-A).

4. Referral guidance - Chronic liver disease

4.1 General considerations

The natural history of cirrhosis and liver disease prognostic scores

In patients with established chronic liver disease/cirrhosis the mortality risks relate to the development of superimposed hepatocellular carcinoma (HCC) and also to problems secondary to portal hypertension. The prognosis of compensated cirrhosis is good, with a median survival of greater than 12 years as compared to around 2 years for patients with decompensated disease (D'Amico 2006). Given this and the fact that, until recently there have been no agents to modify liver fibrogenesis, much work has therefore been done in attempting to anticipate the development of these problems and measures to reduce their risk and thereby improve survival.

An international consensus conference agreed to differentiate cirrhosis into four clinic stages based on the presence of absence of complications related to portal hypertension. Patients defined as having stage 1 cirrhosis have no evidence of varices or ascites and are anticipated to have an annual mortality rate of around 1%. Patients with stage 2 cirrhosis have varices that have not bled and with no ascites. Such patients are thought to have a mortality rate of 3.4%/year and progress to stage 3 or 4 cirrhosis, respectively, by either developing ascites or the varices bleeding. Stage 3 disease, therefore, comprises those individuals with cirrhosis a at the point of their first decompensation. Patients with stage 3 cirrhosis have an approximately 20% annual mortality in this phase. Patients with stage 4 cirrhosis define those that have had a variceal bleed. These patients have a 1-year survival rate of less than 50%, with a major part of the mortality occurring within 6 weeks of the variceal bleed (de Franchis 2005 and D'Amico 2006, de Franchis; Baveno V Faculty 2010).

In the management of individual patients with CLD it is clearly important to be able to accurately define anticipated medium- and long-term outcomes. This issue is of particular relevance in considering when an individual is at significant risk of deterioration and death related to complications of liver disease and hence life-prolonging therapy, such as liver transplantation should be considered. The use of prognostic scores for cirrhosis has been generally used to predict short to medium term mortality risk. The initial Child-Turcotte score, first published in 1964 used in assessing operative risk (Child 1964) was modified and formally categorized into the currently used Child-Pugh score after it was demonstrated to be informative in stratifying mortality risk after oesophageal transection for variceal bleeding (Pugh 1973). The Child-Pugh score (CPS), in addition to using a combination of objective and subjective variables, has well-documented limitations including the fact that the categorization is arbitrary, that measurement of prothrombin time varies between laboratories and that there is a ceiling and floor effect for a number of the variables.

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The CPS, has, however been found to be of great prognostic utility in the context of a number of forms of hepatic decompensation including variceal bleeding and ascites, as well as after TIPS shunt insertion.

The use of objective parameters, measuring continuous variables, has a number of advantages over the CPS and the model for end-stage liver disease (MELD) score, first published in 2000 as a predictor of outcome post-TIPS shunt insertion (Malinchoc 2000) has gained acceptance as a useful predictive tool in a number of different clinical contexts (Kamath 2001). Salerno et al found that MELD was better at predicting 3-month outcome than Child-Pugh (Salerno 2003), though the Child-Pugh score has been found in some studies to be as good as MELD score in predicting outcome after variceal bleeding (Angermayr 2003). MELD has also been found to be predictive of the development of SBP as well as the short-term mortality in established SBP (Nobre 2008 and Obstein 2007). The use of MELD, Na-MELD and UKELD has, however, highlighted inter-laboratory differences between assays, including the INR, as well as the fact that certain well-known issues affect serum creatinine (eg gender, ethnicity, diuretic usage) and serum sodium (eg use of diuretics) (Goulding 2010, Cholongitas 2007a, Cholongitas 2007b).

4.2 Liver Disease Prognostic Scores and listing for Elective Liver Transplantation

A clear understanding of the natural history of cirrhosis and the implications of a change in status of disease is important in determining prognosis and when liver transplantation should be considered, if appropriate. In the UK a predictive model for death on the liver transplant waiting list has been derived and validated using patients historically listed for a first elective liver transplant (2003-2007). The derived model, called UKELD is based on INR, serum sodium, bilirubin and creatinine was found to be a better predictor of mortality than MELD (Barber 2011). The current criteria for placement on the elective liver transplant waiting list in the UK (Box 2) include a UKELD of greater than 49, this being used as the cut-off because it predicts a 1 year mortality risk greater than the 1 year mortality after elective LT. In addition, there are specific clinical forms of decompensation that indicate a poor 1-2 year survival and are not reliably represented adequately by the UKELD score alone. Hence, diuretic-intolerant or diuretic-resistant ascites (DRA) constitutes an indication for listing for LT as does repeated admissions for hepatic encephalopathy and recurrent cholangitis, despite optimal medical management. Variceal bleeding is not, per se, an indication for liver transplantation.

In view of the relatively high 1-year mortality in the context of such decompensation (>9%), patients with chronic liver disease, clinicians involved in the care of patients with CLD should be aware that the development of a decompensation event in a patient should precipitate discussion with the patient/family about the overall prognosis and in parallel an assessment as to whether the patient is potentially a candidate for listing for liver transplantation.

It is at his stage, rather than when waiting for listing criteria are formally reached that discussion should take place with a transplant unit. This then allows appropriate patients to be monitored closely and undergo appropriate evaluation for LT in a timely manner. Equally, it allows patients who are not liver transplant candidates to be given clearer prognostication, important in end-of-life management decisions.

The approach of secondary care liaising with the relevant liver transplant units as outlined above has the additional benefit that an assessment of an individual's co-morbidities can be made at the time of initial decompensation of cirrhosis. For some patients it will be clear that other medical issues preclude LT and the patient can be managed in this context. Factors that may be partially or completely reversible may be picked up at the time of initial decompensation and treatment/modification of these factors might impact on long-term survival and suitability for LT. Such factors include medical issues such as diabetes mellitus, cardiovascular disease and risk factors and respiratory disease as well as other issues such as smoking, illicit drug use, obesity and alcohol. Clearly, however, these issues are best dealt with as early as possible and should therefore be part of compensated as well as decompensated cirrhosis management through a combined approach involving primary and secondary care.

Recommendations

Patients developing decompensated cirrhosis should be discussed with a liver transplant unit (IIa).

Physicians involved in the care of patients with cirrhosis should inform patients of the need to improve all modifiable risk factors.

4.3 Diuretic resistant ascites

The known natural history of cirrhosis suggests that within 10 years of diagnosis 30-50% of patients develop ascites. The prognosis of a patient once they have developed ascites is significantly different from a patient with compensated cirrhosis and the prognosis of ascites differs between those with Child's A, B and C cirrhosis. Gines et al demonstrated that the presence of refractory ascites is associated with a 50% 1-year survival rate (Gines 2004). Refractory ascites is defined as ascites unresponsive to sodium-restricted diet and high-dose diuretic treatment or which recurs rapidly after therapeutic paracentesis (Arroyo 1996). In view of the poor prognosis in the context of refractory ascites (diuretic-resistant or –intolerant), this is an accepted indication for listing for a liver transplant (Rimola 2000). The development of ascites itself is associated with a 40% 2-year mortality (Salerno 1993) and therefore referral for consideration of LT should be made at this point. TIPS shunt insertion is accepted as alternative to large-volume paracentesis in patients with diuretic-resistant ascites. Although successful in treating DRA, there is still controversy as to whether mortality is improved by TIPS shunt, with only one randomised controlled trial showing mortality benefit (Salerno 2004), though a subsequent meta-analysis confirmed this (Salerno 2007).

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Therefore consideration needs to be given to whether TIPS shunt insertion in any given patient will obviate or postpone the need for liver transplantation. In assessing which patients with refractory ascites may have mortality benefit from TIPS shunt insertion without resorting to liver transplantation, recent evidence has found that those patients with a MELD <15 had a median survival of 45 months (Feyssa 2011). Hence, low MELD/UKELD patients with DRA may initially be managed with attempted TIPS shunt insertion.

Recommendation

Patients with cirrhosis who develop diuretic-refractory or diuretic-intolerant ascites should be rapidly referred for consideration of liver transplantation (I-A).

4.4 Chronic hepatic encephalopathy

Chronic HE in the context of chronic liver disease is associated with a poor prognosis (Alvarez 2011). Liver Transplantation can lead to resolution of chronic HE with a good outcome.

Recommendation

Patients with chronic HE or repeated admissions due to recurrent HE that is refractory to optimal medial management should be referred for consideration of LT (I-C).

4.5 Hepatopulmonary syndrome and Portopulmonary hypertension

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) comprises the presence of arterial deoygenation and pulmonary vasodilatation in the context of chronic liver disease. It is important to evaluate the severity of HPS and this is done by the combination of arterial blood gases, transthoracic echocardiography and estimation of the shunt fraction through a technetium-labelled macro-aggregated albumin (MAA) scan. For those with evidence of significant hypoxia, assessment of response to 100% oxygen is important. Because it has been established that the median survival of a cirrhotic patient with HPS is less than 12 months, the presence of HPS is accepted as an indication for listing for LT (Schenck 2003). The severity of HPS is, however, a significant determinant of survival and the presence of an arterial oxygen concentration of ≤50mmHg, in particular with a shunt fraction of over 20% are strongly predictive of post-operative mortality (Arguedas 2003). Hence certain patients may be deemed too high risk for LT simply based on the severity of their HPS.

Given the importance of the diagnosis of HPS, patients with chronic liver disease should be screened for this complication. This can be easily performed by pulse oximetry, with a threshold of oxygen saturations of <96% being a cost-effective cut-off for further investigation, with a sensitivity of 100%, but retaining good specificity at 88% (Arguedas 2007 and Roberts 2007). Furthermore, the evolution of HPS can be monitored effectively by serial pulse oximetry (Kochar 2011).

Recommendation
Patients with hepatopulmonary syndrome should be referred for consideration of liver transplantation (I-C).

Portopulmonary hypertension

Pulmonary hypertension that develops in the context of portal hypertension is called porto-pulmonary hypertension (PPH). The diagnosis is made by the finding of mean pulmonary artery pressure (PAP) of ≥25 mmHg, with an elevated pulmonary vascular resistance (>240 dyn/s/cm) and a normal pulmonary capillary wedge pressure (<15 mmHg) (Bozbass and Eyoboglu 2011). It is generally considered to be less common in cirrhotics than HPS, with a prevalence of 2-10% (Hoeper 2004). The severity of PPH is graded by the MPAP, mild being 25-34mmHg, moderate 35-44mmHg and severe ≥45mmHg (Hoeper 2004). A raised MPAP is known to have a negative impact on prognosis in patients with chronic liver disease (Kawut 2005) and hence in these patients liver transplantation is a consideration. Although the presence of PPH does impart a higher peri-operative risk, mild to moderate PPH does not preclude LT. Indeed, PPH has been found to improve after LT (Bozbass 2009), though can take up to 1 year to do so.

It has been found, however, that severe PPH carries a poor prognosis after LT and is therefore considered a contra-indication to LT (Krowka 2004). Despite this some patients with severe PPH have been found to have a significant improvement in pulmonary haemodynamics on medical therapy such that LT can be performed with decent outcome (Hemnes 2009).

Symptomatically, PPH is difficult to pick up as, if not asymptomatic, may present with non-specific symptoms such as fatigue, pre-syncope, and palpitations in addition to exertional breathless and orthopnoea. Clinician awareness of this complication is important and a low threshold for assessment for possible raised PAP via trans-thoracic doppler echocardiography should exist. This modality has a high sensitivity and specificity in experienced hands (Torregrossa 2001). If suggested on Doppler echocardiography, right-heart catheterization to get formal assessment of mean PAP as well as pulmonary vascular resistance is recommended.

Recommendations

Patients who are found to have porto-pulmonary hypertension should be discussed with a liver transplant unit regarding suitability for the procedure (II-C).

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Liver transplantation is currently contra-indicated in patients found to have severe porto-pulmonary hypertension (MPAP ≥45mmHg). Such patients should nevertheless be discussed with a liver transplant unit and in parallel with referral to a specialist in pulmonary hypertension in order that attempts to treat the PPH are commenced (II-C).

4.6 Specific aetiologies of chronic liver disease

Alcohol

Alcoholic liver disease is the major cause of liver-related death in the UK (ref). There is no UK data to tell us the proportion of patients with advanced alcohol-related liver disease who are discussed with or reviewed by a liver transplant unit. Data that is available suggest that this is in the order of only 5%. (Berlakovitch 2005). Given that there are over 4000 deaths/year in the UK from ALD and that 177 patients with ALD (21.7% of total) were placed on the liver transplant waiting list in 2010-11, this suggests that the vast majority of such patients are dying without discussion with a liver transplant unit, though accurate data on this are currently not available (O'Grady 2006).

This, however, is against a backdrop of a consistent body of literature demonstrating that healthcare professionals, patients and the general public view individuals with ALD as being less deserving of a liver transplant than those considered to have non-self-induced disease (Neuberger 1998 and 2007).

It is clear that, as with all patients with a history of substance misuse, this history and the risks of subsequent behaviour on potential outcome (and utility of any liver graft) need to be fully evaluated as part of the liver transplant assessment process. This aspect is routinely performed in all UK liver transplant centres with such patients. It is this multidisciplinary assessment involving substance misuse specialists, as well as consideration of potential reversibility of decompensated liver disease that constitutes the key elements in the appropriateness and timing of listing for LT. One of the key misconceptions by medical professionals has been the idea that, as part of the gatekeeping for access to a limited resource, there is a rigid '6-month rule' defining a minimum period of alcohol abstinence that has to be achieved before listing for LT can be considered. This is <u>not</u> the case. The rationale for a period of abstinence being desirable derives in the main from the marked improvement seen in even advanced decompensated ALD with avoidance of alcohol. There is also the perspective that the demonstration by an individual of commitment to improving their outcome is indicative of a person who is motivated to modify their lifestyle from a pattern of abusive alcohol intake. However, although there is some evidence an increased duration of abstinence is associated with a lower risk of return to alcohol consumption after liver transplantation (Tandon 2009), there is inconsistent evidence that attaining a 6 month period of abstinence is a reliable means of predicting return to excessive alcohol consumption post-LT (Beresford 2000, Pfizmann 2007, Gedaly 2008 and Karim 2010), this being the only form of return to drinking associated with a worse outcome.

Representatives of the UK liver transplant units met in 2005 and established recommendations regarding liver transplantation for ALD. The issues excluding LT in this context were also discussed and it was concluded that the following factors should preclude listing for LT (Bathgate 2006):

- Alcoholic hepatitis
- Repetitive (more than 2) episodes of non-adherence to medical care (not solely hepatological)
- Return to drinking after professional assessment and advice to the contrary
- Current or consecutive illicit drug use

There are currently no disease-specific indications for LT in patients ALD. A randomised controlled trial in patients with Child's B cirrhosis due to ALD has shown no survival benefit in those immediately listed for liver transplant versus those listed given the current standard of care at the time of listing when Child's C stage was reached (Vanlemmens 2009). In terms of referral to a liver transplant unit, however, the threshold for referral for patients with ALD who have been abstinent from alcohol long-term should be at the point of initial decompensation of their chronic liver disease or when a radiological diagnois of HCC within liver transplant criteria has been made.

There are also two common and more complex scenarios. The first is those individuals who have decompensated after return to alcohol consumption, having had a previous decompensation event and a prolonged spell of abstinence. Such patients, who have been specifically advised to be abstinent at the time of initial liver disease presentation, but who have failed to maintain alcohol avoidance represent a greater concern as to their risk of heavy alcohol consumption post-LT. These patients require, in addition to local alcohol-support programmes, careful multidisciplinary assessment and should be considered on an individual basis. The second is those patients whose first interaction with healthcare professionals regarding consequences of excessive alcohol consumption is at the point of presentation with a severe, protracted decompensation. Ideally the initial decompensation resolves and patients can subsequently manifest a marked improvement in liver function with a period of abstinence. A minority of patients, however, do not improve sufficiently to be discharged over a period of a few months, with ongoing severely impaired hepatic function. For these patients the anticipated improvement in liver function with time does not occur and they do not have the opportunity to prove abstinence at home. This can occur both for severe alcoholic hepatitis and also for decompensated alcohol-related cirrhosis. Severe alcoholic hepatitis is currently regarded as a contra-indication for LT in the UK, although a pilot study is proposed for carefully selected patients not responding to medical management and who have gone through a thorough multidisciplinary assessment. There is evidence from a recently published study from France that in a very carefully selected sub-group of patients decent 2-year outcomes can be obtained after LT in terms of both survival and recidivism (Mathurin 2011). Such patients should be managed in specialist liver units in order to optimise survival chances and early liaison with a transplant unit is recommended in order that, if required, optimal timing of review of the patient by the transplant unit can be planned.

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Patients who have had previous alcohol-related health issues and who subsequently develop advanced decompensated liver disease in the context of return to alcohol consumption or ongoing alcohol misuse are not candidates for referral to a liver transplant unit.

A third, less common, scenario that clinicians struggle with is the patient who at initial diagnosis of ALD, when still drinking, is found to have an HCC within liver transplant listing criteria. In such an instance, although abstinence must be advised and adhered to, the HCC needs to be managed on its own merits in the context of the degree of liver dysfunction.

The above issues highlight the importance of clear and explicit advice regarding complete long-term abstinence from alcohol being given to all patients with alcoholic liver disease at the first point of presentation. This should ideally be supported with a letter to the patient reiterating this and the long-term mortality benefit from doing so.

Recommendations
There are currently no disease-specific indications for liver transplantation in patients with alcohol-related liver disease (IIb)
Patients with non-resolving decompensated ALD should be discussed with a liver transplant unit.
Patients who are found to have hepatocellular carcinoma within transplant criteria at the point of initial diagnosis of ALD (even in the context of recent alcohol consumption) should be referred to the relevant liver transplant unit specialist MDT(II-C).

Non-alcoholic fatty liver disease

The major hepatological consequence of the evolving epidemic of obesity and associated type 2 diabetes has been the marked increase in patients developing end-stage liver disease and/or hepatocellular carcinoma secondary to non-alcoholic steatohepatitis (NASH) (Vernon 2011). This condition currently constitutes 12% of the patients placed on the waiting list for an elective liver transplant in the UK (NHSBT). The natural history of NASH-related cirrhosis is not fully established but available data suggests that around 50% of patients will decompensate within a 10-year period and that the incidence of HCC is 2.6% (Hui 2003 and Ascha 2010). There is no current evidence that either the prognosis after a decompensation event or the natural history of HCC in this context differs from other forms of parenchymal liver disease.

Recommendation
There are currently no disease-specific indications for referral for liver transplantation in patients with NASH-related cirrhosis. As such referral criteria should reflect current referral guidelines for chronic liver disease and/or hepatocellular carcinoma (I-C).

Hepatitis C

There are no good data on the number of people with HCV-related cirrhosis, though is estimated to occur in between 10-40% of people with chronic HCV infection (Afdhal 2004). It is to be anticipated that the much-improved sustained viral responses being reported with newer combinations of therapy including protease inhibitors will result in a reduction of patients developing end-stage liver disease due to HCV.

For a patient who has developed HCV-related cirrhosis, a recent review of the available data indicates that the incidence of decompensation is around 6.4% with an annual rate of death or liver transplantation of 4.6% (Alazawi 2010). In addition, it is well established that there is a relatively high incidence of HCC development in this context, with an incidence of around 4% (Ascha 2010) in individual studies. The fact that the development of HCC in HCV cirrhosis, rather than decompensation is relatively common is borne out by the fact that 11.1% of total patients transplanted with HCV cirrhosis, an additional 22.&% are transplanted with HCC and the majority of these have background HCV (NHSBT).

Once an individual with HCV-related cirrhosis has a decompensation event, it has been felt that the liver disease is too advanced to safely give anti-viral treatment with any anticipation of viral clearance. A recent study has, however, suggested that sustained viral response (SVR) can be obtained in 55% of patients with decompensated cirrhosis due to genotype 2/3 HCV (Iacobellis 2011). In the same study response rates in a few patients with genotypes 1or 4 HCV decompensated disease were poor. Despite this, it is recommended that a decompensation event in a patient with HCV-related cirrhosis should lead to discussion with a liver transplant unit.

Recommendation
Indications for referral for consideration of liver transplantation in patients with HCV-related cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Hepatitis B

The natural history of chronic hepatitis B infection has markedly changed in the context of recent advances in treatment. Decompensated HBV-related cirrhosis is a relatively rare indication for listing for liver transplantation in the UK (0.4% currently), and for the majority of patients with HBV-related cirrhosis considered for LT the indication is the development of HCC (NHSBT). The natural history of compensated HBV-related cirrhosis in the pre-nucleoside/nucleotide analogue therapy era suggested 5-year survival of around 84% as compared to 14% for decompensated disease (Dejongh 1992). More recently, a retrospective study of 161 patients with HBV-related cirrhosis showed 9% of patients developing HCC within 5-year follow-up and 86% survival with 16% of the patients subsequently developing a decompensation event over the 5 years (Fattovich 2002).

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Other studies have, however, reported an annual incidence of HCC in HBV cirrhotics of up to 5% (Fattovich 2004).

Patients with HBV-related cirrhosis require long-term treatment with nucleoside/nucleotide analogue(s) as there is good evidence that good control of replication with HBV DNA suppression improves prognosis and reduces the need for LT (Liaw 2004 and Perillo 2004). Part of the management of a decompensation event in HBV cirrhotics should include the assessment of HBV activity and whether anti-viral resistance has developed.

Recommendation
Indications for referral for consideration of liver transplantation in patients with HBV-related cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

HIV co-infection

Whereas the presence of HIV infection used to be regarded as a relative contra-indication to LT (Devlin and O'Grady, BSG Guidelines 2000), the change in the natural history of patients who have HIV related to HAART, good long-term control of viral replication is often seen. As a consequence, liver-related death is an increasing contributor to mortality in patients with HIV and co-infection with chronic HBV and/or HCV (Rosenthal 2003) and this is no longer regarded as a contra-indication to LT (O'Grady 2005, BHIVA Clinical Guidelines 2010 www.bhiva.org/documents/Guidelines/HepBC/2010/hiv_781.pdf). Therefore patients with complications of advanced liver disease, either decompensation or HCC development, who are HIV seropositive should be considered for liver transplantation. Indeed there is some evidence that rate of progression from initial decompensation to death is accelerated in this patient group (Merchante 2006). Factors that have been found to be associated with a liver-related death over a median follow-up of 20 months were Child-Pugh Score (CPS) ≥ 9 and deterioration of CPS within the follow-up period (Giron-Gonzalez 2007).

Recommendations
HIV-positive patients with cirrhosis should be referred early for transplant assessment, and certainly after the first decompensation (II).
Eligibility for transplantation should be assessed at a transplant centre and in accordance with guidelines for transplantation in HIV-positive patients (II).
There are specific issues that may impact on decision-making regarding LT, including adequate control of viral replication and absence of viral resistance.

Autoimmune hepatitis

Auto-immune hepatitis (AIH), also known as auto-immune chronic active liver disease or AICALD, currently constitutes around 4% of individuals listed for an elective LT in Europe and the US (European Liver Transplant Registry. www.eltr.org and Scientific Registry of Transplant Recipients. www.ustransplant.org). There is a marked female predominance and around 25% are cirrhotic at presentation (Manns and Vergani 2009). Although long-term survival of patients with treated AIH is good, recent data from the UK has demonstrated a standardised mortality rate for liver-related death of 1.63 compared to the general population and a 10-year all-cause survival rate (death or transplantation) of 82% (Hoeroldt 2011). For patients with established cirrhosis secondary to AIH, there is recognised to be an increased risk of development of HCC, though the risk is lower than many other aetiologies and has been found to be around 1.1% per annum in a large cohort followed prospectively (Yeoman 2008), the incident risk being greater for those with a longer duration of cirrhosis.

In addition to presentation in the chronic, insidious form, a significant proportion of patients present with an acute form, which can lead to acute or sub-acute liver failure. The acute, severe presentation, is associated with an increased rate of treatment failure and a worse prognosis (Montano-Loza 2007). The recently published BSG Guidelines recommend referral to a liver transplant unit

Recommendations
Indications for referral for consideration of liver transplantation in patients with auto-immune chronic active liver disease should be in line with agreed criteria for chronic liver disease (I-C).
In patients with liver failure, bridging necrosis on biopsy or in jaundiced patients whose MELD score does not rapidly improve on treatment, contact should be made with a liver transplant centre (I-B).
Patients who are encephalopathic or have ascites in the context of an acute presentation of auto-immune hepatitis, should be discussed with a liver transplant unit (I-C).

Primary Biliary Cirrhosis

Management of primary biliary cirrhosis (PBC) has historically been aided by one of the earliest disease-specific models, the Mayo Clinic model (Dickson 1989, Murtaugh 1994). The Mayo score, comprising age, bilirubin, liver synthetic function as well as a scored assessment of oedema has been demonstrated to be a valid tool to predict outcome, a score of >6 determining significantly worse survival over a 2-year period (Kim 200). The use of the non-disease-specific MELD score and UKELD scores have supervened as the widely used prognostic scores used in patients with PBC as in other forms of chronic liver disease.

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Recommendation
Indications for referral for consideration of liver transplantation in patients with primary biliary cirrhosis should be in line with agreed criteria for chronic liver disease (I-C).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), seen more commonly in males, is thought to evolve to liver failure within a 10-12 year period in those with symptomatic disease (Harnois 1997). More recent data on the natural history of patients with PSC has suggested that time from diagnosis to the time of liver transplantation or liver-related death was 18 years (Ponsioen 2002, review in LaRusso 2006, though it has been proposed that small-duct PSC has a better prognosis than large-duct disease.

Although a number of disease-specific prognostic models have been developed to aid determination of individual patient outcomes (Dicklson 1992, Kim 1999) this remains a challenging condition to determine outcome and hence the timing of listing for LT. Although the same general chronic liver disease indicators are used for listing of patients with PSC, MELD in the US, UKELD in the UK, there is recognition of certain specific issues that can arise in PSC that are not represented by these prognostic scores. The presence of recurrent bacterial cholangitis (refractory to prophylactic antibiotics) secondary to extensive cholangiopathy is accepted as a rare indication for listing for LT.

Recommendations
Indications for referral for consideration of liver transplantation in patients with primary sclerosing cholangitis should be in line with agreed criteria for chronic liver disease (I-C).
The presence of recurrent, refractory bacterial cholangitis in a patient with extensive PSC is also an indication for referral to a liver transplant unit (I-C).
Patients with PSC and proven cholangiocarcinoma should not be referred for liver transplantation (II-C)
Because of the high incidence of colon cancer, regularly scheduled colonoscopies should be performed both before and after transplantation in all patients who have inflammatory bowel disease (II-C).

Haemochromatosis

Hereditary haemochromatosis (HH) is an established cause of cirrhosis with HCC and of end-stage liver disease, with good long-term outcomes (Yu 2007). In addition, undiagnosed hepatic iron overload is found in an additional small number of patients when explant histopathological examination is performed. In many of these patients, the iron overload is an additive or synergistic factor for liver disease/HCC development with HCV, alcohol or NASH.

There is limited data on the natural history of HH-related cirrhosis, though there is good data indicating the increased incidence of HCC in this cohort.

There are clear benefits in de-ironing therapy in terms of risk-reduction for HCC and there may also be benefit in terms of post-transplant outcome. Hence even patients with established cirrhosis due to HH should undergo de-ironing therapy as tolerated. In terms of evaluating fitness for liver transplantation, should HCC develop or decompensation of liver disease occur, particular attention should be given to the cardiac status of the potential recipient as well as to whether sequelae of diabetes impacting on prognosis have occurred.

Recommendations
Indications for referral for consideration of liver transplantation in patients with cirrhosis secondary to hereditary haemochromatosis should be in line with agreed criteria for chronic liver disease (I-C).
Consideration should be given to the diabetic status and possible cardiac involvement in patients with haemochromatosis (I-C).
Consideration should be given to de-ironing patients with haemochromatosis referred for LT (IIa-C).

Alpha1-antitrypsin-related liver disease

Although the frequency of an abnormal alpha1-antitrypsin (A1AT) phenotype is common, even in individuals with the ZZ phenotype, only 10-15% of patients develop chronic liver disease (Perlmutter 1998). A number of different phenotypes can be associated with CLD, though the MZ phenotype with a single abnormal allele, only results in advanced liver disease in the context of an additional co-existent insult, commonly NASH, excess alcohol or chronic HCV infection. As such, although pure A1AT-related liver disease constitutes only X% of patients currently undergoing elective LT in the UK (NHSBT), excess A1AT accumulation is commonly found on explant examination as an unanticipated co-factor in the development in ESLD.

There is currently no treatment for A1AT-related chronic liver disease. As with many forms of cirrhosis, A1AT-related cirrhosis has a demonstrated increased risk of HCC development, particularly in males (Elzouki 19096). There is no data on whether the biology of tumours in this context differs from HCC on the background of other forms of cirrhosis. Therefore screening for HCC should follow standard clinical guidelines for patients with cirrhosis.

Recommendations
Indications for referral for consideration of liver transplantation in patients with cirrhosis secondary to alpha1-antitrypsin accumulation should be in line with agreed criteria for chronic liver disease (I-C).
Patients require detailed lung function assessment prior to transplant and must be told to stop smoking (I-C).

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Cystic Fibrosis

Cystic fibrosis (CF) is known to cause cirrhosis and portal hypertension in the paediatric population as well as young adults. Approximately 5-10% of patients with CF develop advanced liver disease as children, with the prevalence increasing in the second and third decade of life (Debray 2011). Screening for CF-associated liver disease is important in terms of starting specific therapy and also for monitoring for evidence of portal hypertension. It is therefore important that patients with CF are looked after by a multi-disciplinary team involving respiratory physicians and hepatologists.

Indications for liver transplantation in CF can include the development of hepatic failure, but more commonly relate to the development of severe portal hypertension. The timing of LT and therefore referral is crucial in this condition as impaired lung function can deteriorate further as the liver disease deteriorates and progressive decline in pulmonary function in CF can preclude patients with significant liver disease from LT. Patients with advanced CF-associated pulmonary and liver disease have a very poor prognosis and heart-lung-liver transplantation a realistic consideration, with poor outcomes overall (Milkiewicz 2002).

Recommendation
Patients with cystic fibrosis–associated liver disease should be referred early for liver transplantation if there are signs of deterioration of liver function or evidence of significant portal hypertension (I-C).

Wilson's Disease

Wilson's disease (WD) is known to cause both chronic liver disease and acute liver failure (ALF). As discussed earlier, a patient suspected of having ALF secondary to Wilson's disease should be immediately referred to a liver transplant unit. Patients who have a more indolent presentation may be controlled very well for many years if treatment with chelation therapy or zinc is maintained. Such patients can however, decompensate rapidly on cessation of therapy. In such instances, it can be difficult to induce re-compensation of disease with re-institution of medical therapy and liver transplantation may be required. Long-term results of LT for Wilson's disease are good (Arnon 2011). In terms of determining which patients with decompensated WD require LT, the MELD score has shown good predictive power, as has a WD-specific score, the revised Wilson's disease prognostic index or RWPI (Petrasek 2007). However, any form of decompensation of WD should precipitate referral to a liver transplant unit.

Recommendations
Patients with decompensated cirrhosis not responding to chelation treatment should be referred for liver transplantation (I-B).
Patients with acute liver failure should be referred for liver transplantation immediately (I-B).

Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is a very rare indication for liver transplantation, but can result in acute/fulminant liver failure and chronic liver disease with superimposed hepatocellular carcinoma. It is accepted that acute and chronic BCS can be successfully treated by TIPS shunt insertion (Senzolo 2005). Acute or chronic BCS with ascites or encephalopathy should be referred to a liver transplant unit. Liver transplantation for BCS can result in good long-term outcomes (Srinivasan 2002 and Ulrich 2008). The presence of an underlying myeloproliferative disease as part of the cause for the pro-thrombotic state is not considered a contra-indication to LT.

Polycystic liver disease

A small minority of patients with polycystic liver disease will need consideration of either liver transplantation or, if in concert with significant impairment of renal function, a simultaneous liver-kidney transplant. LT should only be considered where other surgical opions are not feasible or there is evidence of associated loss of hepatic function or portal hypertension. The main indication in this context is that of marked abdominal discomfort due to the massive liver volume, with associated anorexia and malnutrition (Kornasiewicz 2008). Hence the standard prognostic liver scores such as MELD are not a good means of monitoring when transplantation should be considered (Arrazola 2006). In patients with suc symptoms who are on or nearing needing dialysis, simultaneous liver-kidney transplantation should be considered.

Although surgically challenging, outcomes after either LT or SLK for polycystic liver disease are good and equivalent to other indications, with an improvement in quality of life (Kirchner 2006 and Van Keimpema 2011).

Recommendations
Patients with polycystic liver disease who have massive hepatomegaly resulting in abdominal pain with poor quality of life should be referred for consideration of liver transplantation. For those patients who have associated renal dysfunction, simultaneous liver-kidney transplantation may be considered (I-C).

Other metabolic liver diseases

Familial amyloid polyneuropathy (FAP)

Familial amyloid polyneuropathy (FAP) associated with transthyretin gene mutations result in progressive and disabling neurological condition. The only known potentially curative treatment for this disorder is liver transplantation as the vast majority of transthyretin is produced by the liver. As such, FAP due to amyloidogenic transthyretin is an accepted indication for LT (Stangou and Hawkins 2004).

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The Porphyrias

Although not required or applicable for the majority of individuals with erythropoietic protoporphyria (EPP), liver transplantation has been performed with variable outcome in a small number of patients with this condition (Anstey 2012). This condition can reach a point where rapidly progressive irreversible liver disease occurs. In such a situation, LT has been used, though specific intra-operative precautions need to be undertaken to avoid severe burns. In addition, it is recognised that LT does not cure the metabolic defect and the condition can recur.

Amongst the acute hepatic forms of porphyria, acute intermittent porphyria (AIP) can present with acute abdominal or neurological events that can occur in increasing frequency. At this rare stage liver transplantation has been used in occasional patients, with resolution of the acute attacks and improvement of neurological symptoms. In this instance, the indication for LT is the poor quality of life with anticipated progressive deterioration with irreversible neurological sequelae, rather than advanced liver disease (Seth 2007). It is recognised, however, that patients with AIP are at increased risk of developing HCC (Andant 1998).

Another form of acute hepatic porphyria, variegate porphyria (VP), presents after puberty with abdominal and neurological symptoms as well as photosensitive bullous skin lesions. There is a single report in the literature of a patient with VP being treated by LT (Stojeba 2004).

Recommendation
For patients with EPP, referral for consideration of LT should be made if there is evidence of jaundice.
Criteria for referral for liver transplantation in acute intermittent porphyria or variegate porphyria are either recurrent refractory attacks of porphyria or a severe attack with neurological deficit despite medical therapy (I-C).

Oxalosis

Simultaneous liver-kidney transplant (SLK) is the recognised treatment modality to cure the genetic defect in type 1 primary hyperoxaluria, with long-term post transplant outcomes equivalent to other indications (Jamieson 1998 and Bergstralh 2010). Most commonly pre-emptive LT or SLK is reuired in childhood, but some individuals start to develop progressive renal failure in late adolescence of early adulthood. SLK ideally prior to the point of starting dialysis, but certainly as soon as possible after commencement of renal replacement therapy is recommended, given the difficulty of clearing the oxalate load once established on dialysis (Lorenzo 2006).

Recommendation
Patients with primary hyperoxaluria with who have evidence of progressive renal impairment should be discussed with a liver transplant unit at an early stage (I-C).

Glycogen storage diseases

GSDs cause metabolic disturbance due to the abnormality of glucose metabolism and glycogen accumulation. GSD represents an indication for liver transplantation (OLT) either when medical treatment fails to control the metabolic dysfunction or there considered to be a high risk of malignant transformation of hepatocellular adenomas (HCA). The most common form of GSD requiring LT is type 1a (Von Gierke's disease) and the long-term outcomes of LT for patients with GSD have been reported to be excellent (Maheshwari 2011).

Recommendation
Patients with glycogen storage disease whose symptoms are not controlled by optimal medical management or who are found on imaging to have developed hepatic adenoma(s) should be referred to a liver transplant unit (IIa-C).

Familial hyperlipidaemia

One known monogenic form of familial hypercholesterolaemia is related to defined mutation in the low-density lipoprotein (LDL) receptor. This is most highly expressed in the liver and as such, liver transplantation has been used in refractory cases with success in term of ameliorating atherosclerosis (Bilheimer 1984, Shrotri 2003 and Popescu 2003).

Miscellaneous

Liver Transplantation can in very instances need to be considered in a variety of lipid storage diseases including Gaucher's disease, Niemann-Pick disease and cholesterol ester storage disease where signs of portal hypertension and parenchymal dysfunction occur.

Atypical haemolytic-uraemic syndrome (HUS) can be due to mutations in complement factor H. In patients with recurrence of HUS after renal transplantation and who are found to have this form of HUS, simultaneous liver-kidney transplant can be considered as this may cure the underlying problem, the transplanted liver acting as a source of complement proteins (Saland 2009).

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5. Monitoring equity of access to transplantation

It is clearly important that all individuals within the UK have the same access to timely and appropriate treatment options irrespective of how the route of access the health-care system or geography. Access to specialist treatment such as liver transplantation is more likely than widely delivered services to vary according to these variables. One of the stated aims of liver transplantation is to minimise disparities in access to this resource and therefore specific indices should be monitored to assess how the system in place functions in this regard. Naturally, data generated must take into account any confounding variables (*eg* regional variations in prevalence of specific forms of liver disease if data is presented geographically). Whilst regional data are available on the prevalences of chronic HBV and HCV infection, this is not the case for many other forms of liver disease. Another means of assessing the burden of advanced liver disease is through analysis of deaths due to chronic liver disease and taking aetiology into account.

In terms of access to LT for cirrhotic patients with HCC, the number of patients listed with or for HCC in the UK is available from NHSBT. This represents the known demand of primary liver cancer on LT resources. For the purposes of monitoring appropriate access to LT for such patients, collated national data from the cancer registry should provide reliable numbers of patients with this diagnosis. It is likely that the information will need to be improved such that it is known whether the HCC occurred on the background of cirrhosis. In addition, discussion of HCC at any specialist MDT will need to generate registration centrally along with information as to whether the patient has been discussed with a liver transplant unit or at a liver transplant tumour SMDT.

The current gatekeepers to listing for liver transplantation are the liver transplant units, whose decisions are taken at their unit MDTs. There are nationally applied listing criteria for listing for which need to be regularly reviewed and modified according to available evidence. As discussed above, determining when LT is contra-indicated/not appropriate in an individual who has life-limiting chronic liver disease can be more difficult to establish. NHSBT currently collects data on all those patients listed for LT, but in order for there to be transparency on the consistency of decision-making at the liver transplant units, key information on those patients who are discussed, but declined listing for LT needs to be registered with NHSBT.

Recommendations

Collection of rolling data on rate of elective and super-urgent liver transplantation by region and by patients' post code.
Linking of this data with data on prevalences of chronic viral liver disease, admissions for chronic liver disease and liver disease mortality data (acute as well as chronic).
Extension of NHSBT data collection to include all patients considered for liver transplantation.

Liver Transplant Units to provide specific information to NHSBT on reasons for decision not to list for transplant. Classification on reasons for refusal to be established in order that these can be analysed.

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