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REVIEW

Adult liver transplantation: A UK clinical guideline - part 1: pre-operation

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ABSTRACT

Liver transplantation is a highly successful treatment for all types of liver failure, some non-liver failure indications and liver cancer. Most referrals come from secondary care. This first part of a two-part guideline outlines who to refer, and how that referral should be made, including patient details and additional issues such as those relevant to alcohol and drug misuse. The process of liver transplant assessment involves the confirmation of the diagnosis and non-reversibility, an evaluation of comorbidities and exclusion of contraindications. Finally, those making it onto the waiting list require monitoring and optimising. Underpinning this process is a need for good communication between patient, their carers, secondary care and the liver transplant service, synchronised by the transplant coordinator. Managing expectation and balancing the uncertainty of organ availability against the inevitable progression of underlying liver disease requires sensitivity and honesty from all healthcare providers and the assessment of palliative care needs is an integral part of this process.

INTRODUCTION

Over just three decades, UK liver transplantation has evolved from the enthusiastic efforts of a few well-intentioned clinicians to a multidisciplinary, closely scrutinised therapy with 1-year survival rates in excess of 90%.[1–3] Despite these excellent outcomes, only a small fraction of the increasing numbers of patients dying of end-stage liver disease will be referred to a liver transplant unit (LTU) for this life-saving procedure.

This two-part guideline is specifically aimed at non-specialist clinicians caring for patients with acute and chronic liver disease (CLD). The first part examines:

- Who to refer for liver transplant (LT).
- How to refer for LT.
- The LT Assessment.
- How to manage the patient on the waiting list.

Part 2 explores the post operative care of the LT recipient.

Further reading includes guidelines from BSG (1999),[4] BASL (2012),[5] EASL Guidelines for LT (2015)[6] and acute liver failure (ALF)[7] and AASLD guideline for LT (2013).[8]

WHO TO REFER FOR LT

Over 90% of LTs in the UK are performed for CLD, where a gradual destruction of liver tissue results in the familiar picture of jaundice, ascites, encephalopathy with coagulopathy and hypoalbuminaemia. A smaller number will have ALF[3 7] and an even smaller number are transplanted for a non-failing liver, where there is survival advantage.[9] This section identifies the reasons, which should prompt either a referral to an LTU or mandate an enquiry.

Acute liver failure

While there are several ALF definitions,[7] the critical elements for the purpose of this guideline, are the three cardinal features of encephalopathy, jaundice and coagulopathy appearing in a patient who, less than 6 months ago, had no evidence of advanced liver disease. The challenge for the generalist in an AMU or emergency department

Table 1 When referral/discussion with the LTU is required for a patient with ALF[7]

Paracetamol induced acute liver failure	Non-paracetamol induced acute liver failure
► Arterial pH <7.30 or HCO_3 <18 ► INR >3.0 on day two or >4.0 thereafter ► Oliguria and/or AKI ► Altered level of consciousness ► Hypoglycaemia ► Elevated arterial lactate (>4 mmol/L) unresponsive to fluid resuscitation	► pH <7.30 or HCO_3 <18mmol/l ► INR >1.8 ► Oliguria/renal failure or Na <130 mmol/L ► Encephalopathy, hypoglycaemia or metabolic acidosis ► Bilirubin >300 umol/L (17.6 mg/dL)

AKI, acute kidney injury; ALF, acute liver failure; CLF, chronic liver failure; INR, international normalised ratio; LT, liver transplantation; LTU, liver transplant unit.

environment is establishing the diagnosis of severe liver injury quickly and minimising the delay in seeking help.[10] Early discussions with LTU enable decisions on comorbidities or contraindications to LT (see below) to be addressed before hepatic encephalopathy develops and safe transfer becomes too high-risk.

Causes of ALF

Despite changes to packaging, paracetamol (acetaminophen) poisoning remains the the most common cause for ALF in the UK.[11] The next most common cause is non-A-to-E hepatitis, then other drug induced liver injuries (prescribed, herbal and proscribed), viral hepatitis and ischaemic hepatitis. Malignancy (primary or secondary), pregnancy (AFLP/HELLP), vascular (including Budd-Chiari Syndrome) and metabolic disorders are rarer causes.

Alcoholic hepatitis is considered in the CLD section, as is acute on chronic liver failure (AoCLF).

When to consider referral/discussion with the LTU in ALF

Once diagnosed, the ALF patient should be managed in an HDU environment and discussed with a LTU (see table 1). Important details include any history of paracetamol ingestion (timing, frequency, 'staggered'), pregnancy, other drugs (prescribed, herbal or proscribed), comorbidity (mental and physical health), laboratory results (including PT, pH, arterial lactate, glucose, renal function, viral screen, autoantibodies and immunoglobulins) and liver imaging. Ideally, patients are safer transferred *before* encephalopathy appears, although there is little published guidance covering this important issue.

Table 1 outlines clinical features in paracetamol and non-paracetamol ALF that correlate with poor outcome and mandate referral. Rarely, non-paracetamol ALF, can present with ascites, deep jaundice and even variceal haemorrhage, where the short history remains the only clue to ALF.

Chronic liver failure

CLF occurs on the background of established liver cirrhosis. The typical clinical features include jaundice, ascites, encephalopathy, sarcopenia along with laboratory features, such as hypoalbuminaemia and coagulopathy, often associated with a rising creatinine and hyponatraemia as liver disease advances. Box 1 describes common causes of CLF.[12]

Acute on chronic liver failure

Acute-on-chronic liver failure (AoCLF) is a syndrome characterised by acute decompensation of CLD associated with organ failures and high short-term mortality. Sepsis, active alcoholism and relapse of chronic viral hepatitis are the most common reported precipitating factors, but still only account for perhaps half the cases, the remainder have no identifiable trigger. The poor prognosis mimics that seen in ALF and mandates an expedited triage and consideration for LT. However, while LT remains the definitive treatment, sadly very few prove suitable.[13]

When to consider referral/discussion with the LTU in CLF or AoCLF

Liver transplantation should be considered, when a patient with established liver disease develops any of the typical features of decompensation (figure 1). As decompensation correlates with rising morbidity and mortality, the supervising clinician should reflect on the key considerations outlined below.

Box 1 Causes of chronic liver failure (CLF)

Causes of CLF:

- Alcohol.*
- Non-alcoholic fatty liver disease.
- Chronic viral hepatitis (B, C and D).
- Autoimmune liver disease (Primary Biliary Cholangitis, Primary Sclerosing Cholangitis, Autoimmune Hepatitis and overlap syndromes).
- Wilson's disease.
- Genetic haemochromatosis.
- Alpha-1 antitrypsin deficiency.
- Secondary sclerosing cholangitis.
- Congenital hepatic fibrosis and other congenital or hereditary liver diseases.

*Alcoholic hepatitis tends to present acutely, frequently with no history of liver disease. Most patients recover with abstinence, but recent studies have demonstrated excellent outcomes with liver transplant in highly selected patients.[44 45]

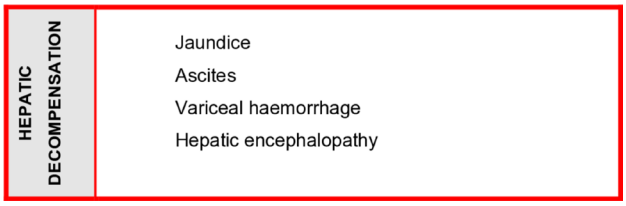

Figure 1 Clinical features of hepatic decompensation.

Key considerations in patients with hepatic decompensation

1. Is the decompensation potentially reversible (for example with abstinence in the case of ALD or with anti-virals in untreated chronic viral hepatitis)* or
2. If not reversible, is the patient suitable for LT*? or
3. Are there any contraindications to LT such as comorbidity which preclude transplant* (see table 5) or
4. If not currently suitable for transplant, could a patient become suitable with treatment or an intervention*?

**If in any doubt, seek advice from local LTU*

Bear in mind that it is possible for a patient to be too unwell for LT *if* the referral is made too late.

To aid with the assessment of suitability for referral, the UK Model for End-Stage Liver Disease (UKELD) score can be calculated. The UKELD score is devised from patient's INR, serum sodium, creatinine and bilirubin (https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/).[14] UKELD scores ≥49 indicate survival advantage for LT over conservative management in patients with irreversible decompensation.

Patients with decompensated CLD, unsuitable for LT, should have this conclusion documented and receive symptom-directed care.

Non-liver failure indications for liver transplantation

Some patients will still benefit from LT, even though their liver is not failing (i.e, likely to cause death within 12 months). This would include patients with cirrhosis and a UKELD score under 49, such as PBC patients with intractable pruritus (see table 2).[5 6 8 15]

HOW TO REFER FOR LT

The next step is referral to the nearest LTU (see online supplementary appendix 1). For ALF patients, a telephone referral is obligatory, but for all other indications, a written referral suffices. Email may speed the referral process, but correspondence with a named individual in LTU encourages collaborative dialogue between referring and transplant physicians. Most referrals for CLD patients come from secondary care hepatologists or gastroenterologists, but referrals are welcomed from any source in primary or secondary care.

What will the LTU want to know?

The LTU will require details of the primary liver disease and its complications, comorbidity, compliance issues, alcohol or drug misuse, family support, previous abdominal surgery and cancer.

A sample transplant assessment tool used is attached as online supplementary appendix 2, but shouldn't replace a letter covering the above issues.

Table 2 Other aetiologies (non-liver failure) suitable for LT[5 6 8 15]

Variant syndromes*	Hepatocellular carcinoma (HCC)†
► Hepatopulmonary syndrome ► Persistent and intractable pruritus ► Polycystic liver disease ► Familial hyperlipidaemia ► Recurrent cholangitis ► Familial amyloidosis ► Hepatic epithelioid haemangioendothelioma ► Nodular regenerative hyperplasia ► Hereditary haemorrhagic Telangectasia ► Ornithine transcarbamylase deficiency ► Glycogen storage disease: symptomatic or presence of hepatic adenoma(s) ► Primary hyperoxaluria: presence of renal impairment ► Porphyria ► Maple syrup urine disease ► Portopulmonary hypertension Consider referral if raised mean pulmonary artery pressure (≥25 mm Hg), PVR >120 dynes/s/cm^{-5}: PCWP <15 mm Hg with clinical response to medical therapy	► Up to 25% of liver transplants in UK have HCC ► Associated with most CLD (HBV, HCV, ALD, NAFLD, autoimmune liver disease, haemochromatosis) and Aflatoxin ingestion ► Current LT selection criteria: – Single tumour <5 cm in diameter, or – Up to five tumours all ≤3 cm, or – Single tumour >5 cm and ≤7 cm in diameter if no progression over 6 months (larger HCC's can be 'downstaged' by local therapies and then considered for transplantation) – AFP <1000

*A variant syndrome is a patient with chronic liver disease whose UKELD score is <49.
†All patients with HCC should be managed within a Liver cancer MDT, which would be expected to recommend referral for liver transplantation as one of the potential 'outcomes'.
AFP, alpha foetoprotein; ALD, alcoholic liver disease; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non alcoholic fatty liver disease; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Table 3 Local investigations and key information to include in referral letter (more details in online supplementary appendices 3–5)

Comorbidity (include all details of pathologies, and important negatives)	Investigations (general investigations as below)	Disease-specific investigations
Cardiovascular	Chest X-ray	PSC: colonoscopy and recent liver imaging
Respiratory	ECG	PBC/AIH: drug history
Renal	Echocardiogram	Hepatitis B: screening tests and viral load
Bone	Oxygen Saturation	Hepatitis C: details of treatment
HIV	Analysis of Ascites	HCC: recent imaging and MDT discussions
Obesity	Endoscopy	PLD/PLKD: brain imaging for Berry aneurysms
Surgical/anaesthetic history	Nutritional assessment	Budd-Chiari syndrome: history of shunts.
Nutrition	Assessment of the performance status	Wilson's disease: details of treatments
Metabolic syndrome	Up to date blood tests and UKELD	Encephalopathy: brain imaging, ammonia, number connection tests
Non-hepatic cancer	Adherence/addiction	
Infectious disease		Ascites: number of drains, episodes of SBP
Social support		Alcohol related liver disease: period of abstinence, engagement with addiction services and so on
Disabilities		
Alcohol and substance abuse		
Mental health		
Smoking		

AIH, Autoimmune Hepatitis; ArLD, Alcohol related Liver Disease; HCC, Hepatocellular Carcinoma; MDT, Multi Disciplinary Team; NG, Naso-gastric; NICE, National Institute for Health & Care Excellence; PBC, Primary Biliary Cholangitis; PLD/PLKD, Polycystic Liver Disease/Polycystic Liver & Kidney Disease; PSC, Primary Sclerosing Cholangitis; SBP, Spontaneous Bacterial Peritonitis; TC, Transplant Co-ordinator.

The quality and content of the referral can influence the pace of transplant assessment. This guide is not intended to be exhaustive, but ensures referrers provide critical information including; general investigations required prior to referral (online supplementary appendix 3); disease specific data required by LTU (online supplementary appendix 4) and comorbidities, psychosocial factors and addiction data that may inform the transplant assessment process (online supplementary appendix 5). All summarised in table 3.

Considerations in patients with alcohol and drug-use disorders

Alcohol

Best practice suggests that patients benefit from early referral to, and engagement with, local addiction services. Repeated non-adherence with documented advice to abstain from alcohol is an absolute contraindication to LT, so all discussions regarding the requirement for lifelong abstinence must be documented and the patient informed of the implication.

The UK Liver Advisory Group[16] and National Institute for Health and Clinical Care Excellence (NICE)[17] have recently updated the policies relating to referral of alcohol related liver disease (ArLD) patients for consideration of LT.

Patients:

- Who are alcohol dependent and continue drinking (even at reduced levels) should not be referred. Referral to alcohol services and engagement is mandatory.
- Who, after 3 months of validated abstinence, still have an indication for liver transplant, should be referred. Validation of abstinence includes random blood alcohol levels, alcohol metabolite testing and support from addiction services.[17]
- Who are abstinent for <3 months, and positively engaged with addiction services, can be referred if there are issues (nutrition, frailty, etc) that might complicate the assessment, or death from liver disease may occur within 3 months.

Thus, there is no absolute rule governing the period of abstinence, other than patients *must* be abstinent at the time of referral. A pragmatic approach is to advise all patients with a failing liver due to alcohol, to become abstinent and engage with addiction services. If there is no immediate indication for referral for LT (as outlined in NICE guidance) then wait for 3 months to observe and if no improvement occurs, refer for LT. If, at 3 months, there is evidence of ongoing liver recovery, then a further 3-month deferment may optimise liver recovery, and also test the patient's commitment to abstinence. At 6 months of abstinence, little further recovery can be expected and referral for LT is appropriate for any patient who remains in liver failure.

Drug addiction/misuse

Drug testing is part of the assessment for such patients. The use of prescribed methadone or buprenorphine replacement therapy does not preclude assessment for LT. However, current use of non-prescribed controlled drugs, addictive medications or 'designer' alternatives precludes referral.

LT ASSESSMENT

On receipt of a referral, the LTU determines whether the assessment requires urgent transfer, elective

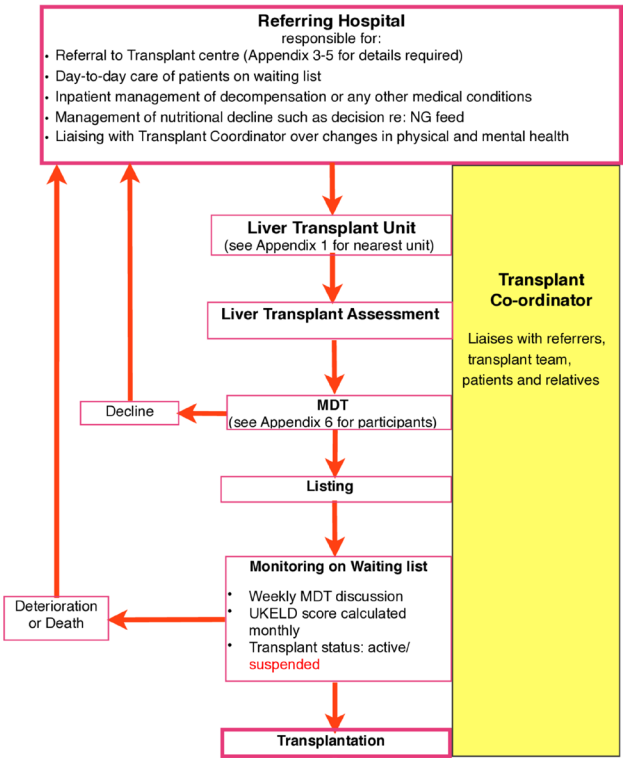

Figure 2 Flow diagram displaying the process of LT assessment from initial referral through workup and listing meeting, to monitoring on the list and either transplant/ death or suspension from the list. The roles and responsibilities of the local unit and the TC are shown. LT, liver transplant; MDT, multi-disciplinary team; NG, naso-gastric; TC, transplant coordinator; UKELD, UK Model for End-Stage Liver Disease

inpatient review, outpatient review or a combination approach. The referral-to-decision times of LTUs should be available for patients and referring hospitals (see figure 2).[18]

The aims of the liver transplant assessment are:

- To confirm the hepatological diagnosis.
- To confirm medical treatment has been optimised.
- To confirm that LT remains the most appropriate option.
- To evaluate mental and physical health comorbidities.
- To identify any contraindications.
- To ensure patients are fully informed of LT.

The transplant assessment is managed by the transplant coordinator (TC) and performed by the core MDT, consisting of physician, surgeon, anaesthetist, social worker, TC and dietician with additional input from pharmacist, addiction specialist, renal physician, oncologist and psychiatrist (see online supplementary appendix 6).

Transplant coordinator

The LT evaluation is supervised by the TC.[19] The TC communicates directly with the patient and family/ support network. This relationship evolves over the assessment process and beyond, depending on progress (figure 2). The TC gains invaluable insight into the candidate.

Table 4 Absolute and relative contra-indications to LT

Absolute contraindications	Relative contraindications*
Untreated HIV*	Inadequate social support
Severe extrahepatic disease with predicted mortality >50% at 5 years including psychiatric disorder	Smoking
Severe irreversible pulmonary disease	Certain anatomical variants
Ongoing alcohol misuse	Extensive previous abdominal surgery
Active illicit drug use	BMI >40 kg/m^2
Certain anatomic variants	Poor clinic attendance and/or adherence
Ongoing extra-hepatic sepsis*	
Active or previous extra-hepatic malignancy†	
Liver cancer outside criteria*	

*These contra-indications can be temporary and require discussion with LTU.
†LT is considered for patients with neuroendocrine tumours (requires referral to national panel).[46]
BMI, body mass index; LT, liver transplant; LTU, liver transplant unit.

As up to 40% of assessments are declined, the TC's role includes advising and supporting such individuals, especially those who assumed referral *automatically* implied acceptance onto the waiting list. For patients accepted onto the waiting list, the TC communicates with patient's referring hospital, GP and community services. The TC provides an explanation of what patients can expect while waiting and when called in for LT.

Indications for LT

The transplant hepatologist confirms the primary liver condition (section 2), makes certain that medical treatment has been optimised, and ensures disease specific investigations are completed (see online supplementary appendices 3-5).

Contraindications to LT

Table 4 describes absolute and relative contraindications to LT.

Conclusion of transplant assessment

MDT decisions

Following assessment, candidates are discussed at the MDT meeting with three potential outcomes: decline, defer, or accept. For those declined, the option of a second opinion, from another transplanting centre, is discussed with the patient and carers either by the hepatologist or the TC. Responsibility for such a further referral rests with the patient's local physician or GP.

Some patients require further optimisation such as nutritional or cardio-respiratory input, prior to activation on the waiting list. Such 'deferred' patients require re-discussion, once the additional elements are addressed.

The remainder of assessments will be 'accepted' and placed on the LT waiting list. The option of live donation will be discussed, if appropriate.

Consent for LT

Consent for LT for candidates who retain mental capacity includes the general guidance for individuals undergoing any clinical intervention (see www.gmc-uk.org). However, the nature and risks of solid organ transplantation, means the process is more complex. Fuller guidance is given by the British Transplantation Society and National Health Service Blood and Transplant (https://bts.org.uk/wpcontent/uploads/2016/09/12_BTS_NHS_Consent_April_2013-1.pdf). LTU's provide oral and written information concerning the risks and benefits of LT for patients and their carers, incorporating outcomes, donor organ related risks (infective, malignant, autoimmune, metabolic and others), procedure risks, disease recurrence and the need for adherence and life-long follow-up. The right to decline certain organs is carefully discussed (see Part 2, figure 1).

HOW TO MANAGE THE PATIENT ON THE WAITING LIST

Waiting list

During 2015–2016, 1161 patients joined the LT waiting list in the UK. At 1-year post-registration, 73% of patients had received a LT, 9% had died waiting or been removed due to deterioration. A further 4% were removed for other reasons such as clinical improvement, non-compliance or at patient's request. The remaining 14% were still waiting.[3]

The waiting times depend on several factors, including recipient blood group, size and illness severity (i.e. UKELD score). The median waiting time is currently 135 days, though this is shorter for recipients who are blood group AB (56 days), A (84 days) and B (129 days) than blood group O (256 days).[3] Details of organ allocation are outlined in Part 2.

Monitoring on the waiting list

Patients listed for LT must be monitored closely for changes in their clinical circumstances. The 'local' team manage *all* the patient's routine care, but as this may impact on their suitability for LT, regular and careful communication with the LTU, via the TC is essential (see figure 2).

Optimisation of patients on the waiting list

Managing deterioration

Patients on the LT waiting list frequently present with decompensation to their referring hospital. This decompensation carries a significant mortality risk.[20]

The Lancet Standing Commission on Liver Disease has highlighted the need to focus on improving the care for acutely ill, hospitalised patients with liver disease.[21] Ideally, hospitals should have in place a 'care bundle' for patients admitted with decompensated cirrhosis.[22]

Management of listed patients in the referring hospital

Patients on LT waiting list require monthly review in gastroenterology/hepatology outpatient clinics for nutritional review, blood-sampling, UKELD calculation and surveillance tests for cirrhosis. The LTU should be appraised of any deterioration, as listing status may need reviewing. Transfer to the LTU for acute deterioration is sometimes necessary, but if not, the confidence of patients and their carers is enhanced when there is open dialogue between the local hospital and the LTU.

Nutrition

Most patients with end-stage cirrhosis are malnourished[23] and malnutrition in recipients predicts poorer outcome after LT.[24 25] LTUs recommend a nutritional supplement for patients on the waiting list for the beneficial effect on anthropomorphic indices.[26] Obesity is increasingly common among patients on the waiting list for LT. Sarcopenic obesity, or severe muscle depletion in the setting of obesity, is reported in almost half of obese patients with cirrhosis and is associated with an increased risk of pre-LT mortality. For patients with compensated cirrhosis, traditional lifestyle modifications are safe, but very low calorie diets (<1000 calories/day) are not safe. For decompensated cirrhotics, low-calorie diets may exacerbate sarcopenia and malnutrition, so such patients should maintain caloric intake with higher protein, nutrient-rich foods.[27]

Exercise

There is little data on exercise in patients waiting for LT. However, exercise programmes known as 'prehabilitation' can improve functional capacity and postoperative outcomes in patients with liver disease awaiting major surgery.[28] Recently, the Birmingham group published a proposal to clarify this issue in patients awaiting LT.[29] Most centres advise a sustained exercise target of up to 25 minutes daily, depending on the individual patients pre-existing activity levels and physical impairments. A step-counter (available as an app) is helpful for target setting and the Birmingham team's proposal also incorporates specific advice on functional resistance exercise training that can readily be carried out at home.[29]

Other lifestyle factors

Lifestyle factors are central to survival both on the waiting list and beyond. Patients should be supported to make positive and sustainable lifestyle behaviour changes.

Active engagement with alcohol services is key for any ArLD patient and this may be a condition for listing. Alcohol use rates of 15%–25% have been reported for patients on LT waiting lists so ongoing monitoring (blood, urine, breath or hair) and support are essential.[30] Most centres require random testing

for patients listed for ArLD and will liaise with the local hospital to facilitate timing and frequency.

Active smoking increases all-cause mortality at 5 and 10 years after LT[31] due to additional surgical complications, more cardiovascular disease, sepsis and solid-organ malignancy.[31–34] Smokers must engage in a smoking cessation programme and if smoking cessation is a condition for listing, patients should expect carbon monoxide breath-testing.

Psychosocial support

Patients listed for LT have high rates of psychological distress and depression which reduces quality of life, adaptive coping and functional status.[35] Significant depression reduces pretransplant survival.[36] Waiting times, concern about deterioration, organ scarcity and false-alarms contribute to patient anxiety. All patients require screening for depression and management accordingly.

Patients and carers receive education, including attendance at patient information sessions at the time of listing. This should include access to 'expert patients', information on LT services, the patient pathway, support groups and services offering psychological, social and spiritual/cultural support. The LTU have a transplant healthcare professional available 24/7 for telephone advice for patients and carers and ongoing contact with TC, specialist nurses and a social worker, as necessary.

PALLIATIVE CARE AND LT

Liver transplantation is the gold standard treatment for many patients with ALF, CLF and liver cancer, however, almost half of those assessed are declined and 20% patients die while waiting, meaning four people die for every one transplanted. Patients with CLD have a variable level of access to palliative care services, which can vary in quality.[37 38]

By definition, those listed for LT have advanced disease and therefore, concomitant physical and psychosocial issues. Patients suffer from a high physical symptom burden[39 40]; symptoms are often complex and dramatic, frequently necessitating hospital admission[41] with a poor evidence base to support the use of many drugs. Patients also suffer complex psychosocial issues including the stigma of liver disease, complex socioeconomic background circumstances and uncertainty associated with the potential for re-compensation and the possibility of transplantation.

Maintaining hope while ensuring an appropriate holistic assessment of the patient's needs is challenging for everyone involved in delivering care. Discussions on end-of-life care including preferences, is an essential component in the management of patients with advanced liver disease, including those awaiting LT.

Early palliative care intervention can improve quality of life by improving symptom burden and mood, alongside less aggressive treatment and a reduction in hospitalisation.[42 43] An assessment of palliative care needs should form an integral part of any transplant assessment process. Collaborative working is essential at a time of such great uncertainty if the overall quality of life for these patients and their carers is to be improved.

Key points

- Consider all patients with decompensated CLD for liver transplantation
- Discuss all ALF patients with LTU
- Provide LTU with details of primary liver disease and co-morbidities in mental & physical health
- Patients on transplant waiting list are the shared responsibility of referrer and LTU
- The palliative care needs of the patient are a critical part of the transplant assessment process.

CONCLUSIONS

- All patients with decompensated CLD, should be considered for LT.
- All ALF patients should be discussed with the LTU and transferred in timely fashion, if appropriate.
- LT may be considered for variant syndromes, HCC and various other non-liver failure indications after discussion with LT team.
- The LTU require details of diagnosis, comorbidity, nutritional status and frailty in order to complete evaluation.
- Patients on the LT waiting list are shared between the referring centre and LTU. Good communication between the various healthcare professionals is critical. For patients who deteriorate, candid discussions with individuals and their relatives coupled with timely utilisation of palliative care services should optimise outcome for all concerned.

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She co-wrote the section on the Immunosuppression agents in Part 2 with Prof Neuberger and gave input into Part 1 particularly with the 'disease specific considerations' and where medication interactions can occur. MC (consultant transplant hepatologist): Co-authored the section on 'Management of the patient on the waiting list' and then read both Part 1 and 2 of final submission as an additional critique for all sections. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval. AH (consultant transplant hepatologist): Co-authored the section on 'How to refer', and then drew up the tables and added valuable additional input, as well as re-write participation for the sections, when the original submission was too lengthy. Critical role in planning, final manuscript editing and approval. SH is a consultant histopathologist and wrote the section on cellular rejection in Part 2. He added valuable oversight in Part 1, particularly as both parts were too lengthy and required significant reduction in word count. JH (consultant hepatologist in a DGH) wrote the section on Transplant assessment and with KJ refined this section, to focus on the DGH referrer. JH also read both completed parts to provide the DGH perspective on these elements of liver transplantation and ensure focus was correct for that audience. Critical role in planning and acquisition of data for inclusion into Part 1 of guideline, along with evaluation of relevance to project. Part 1 and 2 final manuscript editing and approval. KJ (Transplant co-ordinator) provided section on the Transplant co-ordinator and then gave critical input for aspects on process of organ selection along with RP (below). Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval JL (consultant transplant hepatologist) co-authored the section on 'How to refer' and provided editorial input for part 2. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval SM (consultant transplant hepatologist) co-authored the section on 'How to manage the patient on the waiting list' bringing together the co-ordinators input with the transplant centre and the interaction with secondary care referring centre. Providing insights from both sides of the secondary/tertiary care interaction and then editing the initial contribution of the section to a more manageable section. Ensuring relevance of data collected for the project along with final manuscript editing and approval KM (consultant transplant surgeon) contributed to the section in part 2 on Transplant surgery and outcomes. KM also provided input in Part 1 into section on Transplant assessment and previous surgery. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval DM (consultant transplant surgeon) co-authored the section on Transplant surgery with KM and post-transplant surgical complications. He also provided input in Part 1 into section on Transplant assessment and previous surgery. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval JN (consultant transplant hepatologist) wrote the section on Post-Transplant Immunosuppression with the aid of A Considine. Prof Neuberger also contributed to the Part 1 in editorial role, when he helped with the original concept, he provided a critical role following the original guideline production and prior to it's splitting into two halves (Part 1 and 2) and ensuring correct focus was maintained when the manuscript was reduced in size. RP (consultant transplant surgeon) wrote the section on organ allocation and donation. He also made a significant contribution to the post-operative care and complications sections and the pre-op evaluation (Part 1). Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval AP (Liver Pharmacist) contributed to Part 2 immunosuppression section, but also gave useful input into Part 1 and 2 from point of view of medication and drug interactions, particularly with viral hepatitis treatment. Critical role in evaluating data for inclusion into guideline, along with maintain relevance to project. Final manuscript editing and approval WP (Consultant in Palliative Care) authored the section on Palliative Care and Transplantation in Part 1. Her contribution in Part 2 was proof-reading and providing critical input. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval LS is a Transplant co-ordinator. She contributed to the section on How to refer a patient for liver transplant (Part 1) and gave input into section on Organ allocation (Part 2). Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval KS (consultant transplant hepatologist) wrote the section on 'When to refer' in Part 1, but also gave significant editorial input to entire project, at the time of the section merge and subsequent division into two halves. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval DT and RW (consultant transplant hepatologists) co-authored the section on Transplant outcomes. They provided critical input into Part 1 as well, with respect to referral process. Critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project. Final manuscript editing and approval. DT (consultant transplant hepatologist) co-authored the section on Postoperative care and complications (non-surgical). DT also supported the entire process by helping the lead author with editing sections and discussion of tables, pictures, deciding on section inclusion, data relevance and final manuscript editing and approval.

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Appendix 1: UK & IRELAND TRANSPLANT CENTRES

TRANSPLANT CENTRE	**ADDRESS**	Contacts
Birmingham	Queen Elizabeth Hospital Birmingham Mindelsohn Way Edgbaston, Birmingham B15 2GW	Tel: 0121 371 4414 Email: hpbsurgeons @uhb.nhs.uk
Cambridge	Cambridge University Hospitals NHS Foundation Trust Cambridge Biomedical Campus Hills Road Cambridge CB2 0QQ	Tel: 01223 216 672 Email: liver.coordinators@addenbrookes.nhs.uk
Dublin	St Rita's Building St Vincent's University Hospital Elm Park Dublin 4	Tel: 012214248 Email: Liversecretary @svuh.ie
Edinburgh	Edinburgh Royal Infirmary 51 Little France Cres, Edinburgh EH16 4SA	Tel: 0131 242 1721 Email: sltu@nhslothian.scot.nhs.uk
King's	Institute of Liver Studies 3rd Floor, Cheyne Wing King's College Hospital Denmark Hill London SE5 9RS	Tel: 020 3299 1766 Email: kch-tr.liveroutpatients @nhs.net
Leeds	St James's University Hospital Beckett Street Leeds LS9 7TF	Tel: 0113 2066585 leedsth-tr.livertransplant @nhs.net
Newcastle	Institute of Transplantation Freeman Hospital Freeman Road High Heaton Newcastle upon Tyne NE7 7DN	Tel: 0191 244 8068 Email: tnu-tr.CadavericRenalDonor@nhs.uk
Royal Free	Pond St, Hampstead, London NW3 2QG	Tel: 020 7794 0500 ext: 36896 Email: rf.ltxc@nhs.net

Appendix 2: **Transplant Assessment Proforma**

DIAGNOSIS			
CO-MORBIDITY			
BLOOD TESTS: (*within 1 month of referral)			
Blood Group		BMI kg/m^2	
MELD	UKELD	C-P	*GFR mls/min
*Bil umol/L	*Alb g/L	*ALP IU/L	*ALT U/L
*PT secs	*Hb g/L	*PLT x10^9/L	*WBC x10^9/L
*Creat umol/L	*Urea mmol/L	*Na^+ mmol/L	*K^+ mmol/L
Ferritin ug/L	B12 ng/L	Folate ug/L	
ANA	AMA	SMA	
HBV	HCV	HIV	CMV
Glucose mmol/L	tTG	AFP kU/L	A1AT
IgM g/L	IgA g/L	IgG g/L	
TSH mu/L		MRSA	
*PaO_2 (FiO2 %) kPa		*$PaCO_2$ kPa	
CARDIORESPIRATORY etc:			
FEV1 L	FVC L	FEV1/FVC	
Echocardiogram: (date / /)			
ECG: (date / /)		CXR: (date / /)	
CPEX: (date / /)			
IMAGING:			
USS Liver: (date / /) Portal vein Patent Y/N, Ascites Y/N, HCC Y/N			
MRI: (date / /)			
CT: (date / /)			
GASTROSCOPY: (date / /)			
DIETICIAN:			
Notes:			
Handgrip kg	MAMC cm	RFS	
DRUG HISTORY:	**ALCOHOL/ADDICTION**	**SOCIAL SUPPORT etc:**	
NOTES:			

**Colonoscopy within 12 months if PSC

Appendix 3. General investigations to be completed before patients are referred for assessment.

INVESTIGATION	WHY IS THE TEST REQUIRED?
Chest X-ray	Normal/Cardiomegaly/Pulmonary hypertension/Effusion/Metastases (in HCC patients)
ECG	Normal/Ischaemic changes/Right or left ventricular enlargement/Right heart strain/Conduction block and rhythm disturbance. A prolonged QTc is often seen in cirrhosis.
Echocardiogram	Echocardiogram is mandated in patients in whom TIPSS is being considered. Note signs of diastolic and valvular dysfunction. Systolic function is often over-exaggerated by the hyperdynamic circulation.
Oxygen Saturation	Low oxygen saturation can be a feature of hepatopulmonary and/or porto-pulmonary syndromes or may indicate parenchymal lung disease.
Analysis of Ascites	All patients with ascites should have analysis for protein levels, SAAG gradient, cell counts and differential, cytology and culture (including Tb in at risk patients) and antibiotic prophylaxis offered if indicated.
Endoscopy	All PSC referrals should have had a recent colonoscopy if safe. All referrals should have had a gastroscopy for varices assessment and consideration of prophylaxis
Nutritional Assessment	Malnutrition and sarcopenia are commonplace in end-stage liver failure. All patients should be assessed by dieticians for an assessment of their nutritional state
Assessment of the performance status	Some patients are unfit for transplantation and need extensive pre-conditioning work-up to improve their peri-operative morbidity
Up to date blood tests and UKELD	Patients are stratified on the waiting lists according to their UKELD score so up to date blood work allows for prioritisation [https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/]
Adherence/Addiction	Any concerns with regard to adherence, clinic attendance and/or engagement should be highlighted at an early stage. See above

Appendix 4. Disease specific considerations in assessment

DISEASE	Referring centre	Transplant Centre
PSC	PSC patients should have had colonoscopy in the last 12 months. The right colon must be visualised as colorectal cancer is increased in this patient group. Recent cross-sectional imaging should be sent	Transplant indication includes recurrent cholangitis and sepsis. PSC patients with IBD must have IBD optimised as poorly controlled colitis pre-transplant negatively impacts on graft survival.
PBC/AIH	Include a full drug history including immunosuppression, drug intolerance and any reasons for withdrawal.	
Hepatitis B	Screen all candidates for HBV (HBsAg, HBeAg, HBcAb). All HBV sAg +ves, require viral load and HDV status. Include medication history	Consider vaccination for all sero-negatives. Previous contact with HBV requires testing for HBV DNA as detectable HBV DNA will require suppression, pre-transplant. Patients transplanted for HBV disease, will receive HBIg and nucleos(t)ide analogues peri- and post transplant, according to local protocols.
Hepatitis C	If PCR positive, genotype, viral load and treatment history should be provided. Whilst all patients with a failing liver should be discussed with a LTU, most will recommend eradication therapy prior to surgery for patients with MELD scores $\leq$20, and vice versa for MELD score >20	DAAs have reduced the number of patients requiring liver transplant and up to 25% listed with MELD <20 will improve and be-de-listed, after eradication of virus.
HCC	Recent imaging, notes from HPB MDT discussions, any previous loco-regional therapy (including dates) and information pertaining to response and tumour size/load prior to treatment, must be included Cancer staging and monitoring protocols vary from unit to unit.	In the UK, most LTUs use Milan criteria or adapted version called the “extended Milan criteria”. The Milan Criteria specify that optimal transplant outcome are achieved with either one HCC lesion <5cm or three lesions, each less than 3cm and no evidence of metastases. ‘Down-sizing’ with local therapies, is allowed but requires careful radiological evaluation and usually depends upon agreement across centres, on a case by case basis.
PLD/PLKD	MRI/MR Angiogram of brain to exclude berry aneurysms.	
Alcohol related Liver Disease	A six month period of abstinence is recommended *before* listing to optimise liver recovery, and to test the patient’s commitment to abstinence. However, NICE	1. All patients referred for liver transplantation receive a full psycho-social evaluation. 2. A further structured substance misuse evaluation with

	recommends referral after 3 months of abstinence to allow for the period of evaluation and waiting and minimise the chance of the patient deteriorating beyond transplantation.	additional psychiatric evaluation is usually carried out. 3. Also, patients will be requested to sign a contract in the presence of family to adhere to abstinence after transplant.
Budd-Chiari syndrome	The LTU will require all records of discussions with regional HPB unit, historical shunting procedures, surgery etc as well as details of procoagulant disorders tested for.	BCS management consists of trying to re-establish venous drainage of the liver and resorting to transplant only if stents and shunts have failed. The more severe and acute the presentation the more likely that transplantation will be necessary.
Wilson's disease	Wilson's disease may present as either acute liver failure as well as decompensated chronic liver disease in patients who did not respond to medical therapy.	Patients and family should know that liver transplantation cures the liver disease and underlying metabolic disturbance, but not the neuropsychological features
Encephalopathy	Provide relevant brain imaging (MRI preferably). If diagnostic doubt persists provide EEG reports and/or blood ammonia measurements. Detail any hospital admissions with hepatic encephalopathy.	
Ascites	Detail the number and frequency of ascitic drains and whether there has been evidence of SBP. Describe complications such as loculated ascites, hydrothorax and/or haemorrhage.	

Appendix 5: Co-morbidity

CO-MORBIDITY	RELEVANCE
Cardiovascular	Cardiomyopathy is seen with cirrhosis and alcohol. Several liver-lung syndromes (HPS/PPHT/HHT) are described. A clinical history, contrast echocardiography and other invasive tests may be necessary. Any history of cerebrovascular disease should be sought and described i.e. haemorrhagic/embolic/infarct and relevant imaging and investigations supplied.
Respiratory	All respiratory disease and investigations should be described, including any ITU admissions and performance status. For hypoxic patient, include cross-sectional imaging, lung function, transfer studies and tests looking for PEs/Shunts & AVMs
Renal	For patients with chronic kidney disease (CKD) include investigations and treatments. If the eGFR <30mls/min/1.73m^2 for more than 3 months, a combined liver kidney graft may be necessary. Urinalysis, Albumin to Creatinine ration (ACR), renal ultrasound and cultures should be completed in all patients with an eGFR <60mls/min/1.73m^2 .
Bone	Assess the FRAX score in all patients (https://www.shef.ac.uk/FRAX/tool.jsp)
HIV	HIV on treatment, is not a contraindication to liver transplantation. Enclose details from specialist teams of treatment history, adherence and drug prescription.
Obesity	Record BMI and estimate dry BMI if ascites present. BMI>40kg/m^2 is a relative contraindication
Surgical/Anaesthetic	All surgical history should be detailed in the referral letter
Nutrition	A dietetic assessment prior to referral is mandatory. Offer appropriate nutritional support (e.g. protein supplements and/or NGT feeding)
Metabolic Syndrome	Request an HbA1c (note anHbA1c may be artificially low in patients with chronic anaemia) For diabetes, document the duration, time on treatment (including years on insulin therapy), urinalysis, eye examination & fundoscopy, vascular complications. Record other components of metabolic syndrome such as hypertension and dyslipidaemia.
Non-hepatic cancer	A history of cancer may not be a contraindication Details of dates of diagnosis, staging, treatment, prognosis, 5 year survival and correspondence from treating oncologist
Infectious Disease	Any communicable disease (including TB) in the patient and household contacts should be reported
Social Support	Housing, next of kin, adherence with appointments, tests and therapies should be included in the referral letter
Disabilities	Learning disabilities or deafness/ visual impairment does not prevent assessment for transplantation
Alcohol & substance abuse	Alcohol, illicit and prescribed drug usage including analgesics and sedatives, must be reported
Mental health	Prior history and treatment for mental illness, including self-harm should be detailed in the referral letter
Smoking	Active smokers should be advised to stop and be referred to smoking cessation service

Appendix 6: The Liver Transplant Multi-disciplinary Assessment (Co-ordinated and overseen by Transplant Co-ordinator)

The Medical Assessment:		
Hepatologist	General health	Past medical history, current (non hepatological) medical issues, medication etc (see Table 3)
	Liver disease	Confirm history of liver disease, diagnosis, management and current treatment. Disease-specific evaluations (see Table 4) (If hepatocellular cancer present, oncology input)
	Drug History	To include allergies
	Urine tests	Glucose, protein, drug-screen (if relevant)
	Blood tests	Liver tests (non-invasive liver screen, synthetic function), renal function, viral screen blood-typing
	Cardio-pulmonary	ECG, PFTs and echocardiography (if not recently performed). Further testing, such as stress testing etc with advice from cardiologist (see Tables 3)
	Radiology	CXR, USS liver and CT/MRI depending on indication etc (see Tables 3)
	Cancer risk	Breast/Colon/Cervix where appropriate
	Latent infection	CMV status pre-transplant and post transplant prophylaxis HBV etc HIV status and treatment related issues
	Explanation	Explanation of process, all outcomes etc
The Surgical Assessment:		
Surgical team		Confirm liver transplant is indicated. Surgical issues: previous abdominal surgery, obesity, portal vein compromise, anatomical variants Discussion of procedure, risks, complications and organ issues.
The Dietetic Assessment		
Dietician		Assess nutritional status, including anthropometry Assess patient (and family) understanding of nutritional advice. Co-ordinate with dietetic service at referring hospital
The Anaesthetic Assessment		
Anaesthetist		Previous anaesthetic issues. Standard tests include Pulmonary function tests and Oxygen saturation. Risk assessment including specific cardiopulmonary issues. May request CPEX or DSE etc Discussion with patient/family over ICU, surgery process etc
The Psychosocial Assessment		
Social Worker		Psychosocial issues, family/support mechanisms, effect on dependants etc
Addiction specialist		Tobacco, alcohol and illicit drug dependencies
Psychologist		Mental health issues, addiction support etc