PART 1

When to Refer a Patient for Liver Transplantation

CHAPTER 1
General Considerations

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Key points

- Early referral to a transplant centre is important.
- Criteria for referral depend on the clinical context (acute liver failure, subacute liver failure, chronic liver disease, liver cancer).
- Refer paracetamol hepatotoxicity when pH < 7.4, lactate > 2.5 mmol/L, renal impairment or encephalopathy, and all non-paracetamol acute or subacute liver failure cases at time of recognition of diagnosis and/or when INR > 1.5, creatinine > 50 mmol/L, evidence of organ failure or encephalopathy.
- Refer all cirrhotic patients found to have liver lesion(s) characteristic of hepatocellular carcinoma to a multidisciplinary team meeting in institutions where liver transplantation and other modalities are available.
- Refer patients with chronic liver disease to a transplant centre when they develop a first episode of decompensation (ascites or hepatic encephalopathy), those who develop diuretic-refractory or -intolerant ascites or type 1 hepatorenal syndrome, and patients with chronic hepatic encephalopathy or repeated admissions due to recurrent hepatic encephalopathy.
- Refer patients when they develop Child-Pugh score ≥ 8, MELD score ≥ 10 and UKELD score ≥ 49 unless contraindications exist.
- Patients with hepato-pulmonary syndrome and those found to have porto-pulmonary hypertension can also be considered for transplantation.
- Assessment and management of substance misuse and risks of alcohol recidivism require a team specialised in addictive behaviours. Decisions as to suitability for liver transplantation are best undertaken by transplant centres.

General principles

Clinical guidelines for referral of patients for liver transplantation (LT) from the United Kingdom, the United States and Europe emphasise a number of important general considerations.

Liver Transplantation: Clinical Assessment and Management, First Edition.
Edited by James Neuberger, James Ferguson, and Philip N. Newsome.

- It is necessary to ensure that a potential transplant candidate is sick enough to justify liver transplantation and that all other measures to manage their disease have been exhausted.
- It is necessary to assess whether the patient (1) is fit enough to survive the procedure, (2) will be compliant with medication and advice, and (3) does not have comorbidities that will impact on survival or quality of life.

This chapter will consider those issues with respect to a number of clinical indications and specific concerns in these patients.

All guidelines emphasise the importance of early referral to a transplant centre. This allows time for the transplant centre to assess the patient fully, and gives the potential candidate and their family an opportunity to review all their clinical options and to make decisions without pressure. Late referral may jeopardise post-transplant outcomes as pre-transplant status is one important factor dictating post-transplant hospital stay and mortality.

Referral can be considered in a number of categories: acute liver failure; chronic liver disease; hepatocellular carcinoma (HCC); and variant syndromes.

Acute liver failure: paracetamol hepatotoxicity

The importance of early referral in cases with paracetamol-induced hepatotoxicity cannot be overemphasised. Early discussion with a liver transplant centre will allow timely transfer of patients and expedite diagnostic evaluation by the transplant team. Prognosis is better in those transplanted earlier with lower grades of encephalopathy, emphasising the importance of early transfer. Early referral also facilitates advice on stabilisation of the patient before transfer and avoids unnecessary transfer of patients who will not come near to meeting transplant criteria.

A number of factors predictive of poor prognosis are relevant when considering referral in individual cases (Table 1.1).

- The King's College criteria continue to demonstrate high specificity for mortality in meta-analyses but has low sensitivity.
- Elevated serum lactate is also a marker of poor prognosis but again has low sensitivity.
- Later markers of poor prognosis include renal impairment, hepatic encephalopathy, increasing age, malnutrition, a staggered overdose, and prior alcohol use.

Referral summary

Refer patients with paracetamol ingestion with evidence of:

- pH < 7.4 at any time after ingestion;
- elevated serum lactate > 2.5 mmol/L after fluid resuscitation;

Table 1.1 Referral and transplant criteria in patients with acute liver failure

	Referral criteria	Transplant criteria
Paracetamol	pH < 7.4 at any time after ingestion	pH < 7.25 > 24 hours after overdose and after fluid resuscitation
	Serum lactate > 2.5 mmol/L after fluid resuscitation	Serum lactate > 3.5 mmol/L > 24 h after overdose on admission or > 3.0 mmol/L after fluid resuscitation
	Any evidence of prolonged prothrombin time, renal impairment or encephalopathy	INR > 6.5 + creatinine > 300 μmol/L or anuria, + grade 3/4 encephalopathy
Non-paracetamol	Any grade of encephalopathy	Seronegative hepatitis, hepatitis A, hepatitis B, drug-induced liver failure. Any 3 from: unfavourable aetiology; age > 40 y; jaundice to encephalopathy > 7 days; bilirubin > 300 mmol/L; INR > 3.5
	INR > 1.5 or creatinine > 150 mmol/L	Seronegative hepatitis, hepatitis A, hepatitis B, drug-induced liver failure, INR > 6.5 or PT > 100 s
		Acute presentation of Wilson's disease, Budd-Chiari syndrome, autoimmune hepatitis. A combination of coagulopathy and any grade of encephalopathy
		INR > 1.5 and any grade of encephalopathy

- prolonged prothrombin time, renal impairment or hepatic encephalopathy.

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

Acute liver failure: non-paracetamol aetiologies

Clinical and laboratory criteria (Table 1.1) defining a poor prognosis in non-paracetamol ALF are well described. The rate of progression to severe stages of hepatic encephalopathy is slower than in paracetamol-induced ALF but is also less easy to predict at an early stage. ALF with encephalopathy in the context of certain rarer aetiologies including autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome, pregnancy or lymphoma should always be discussed with a transplant centre.

Late-onset hepatic failure has a particularly poor prognosis and the diagnosis should initiate an immediate consultation with a transplant centre.

Referral summary

Refer patients with non-paracetamol ALF in the presence of:

- the development of any grade of encephalopathy;
- coagulopathy with INR > 1.5 or serum creatinine > 150 mmol/L;
- any other additional organ failure;
- severe acute presentation of auto-immune hepatitis with encephalopathy or ascites;
- coagulopathy and encephalopathy-associated Wilson's disease;
- a diagnosis of late-onset hepatic failure with encephalopathy.

Hepatocellular carcinoma

In Western societies around 95% of hepatocellular carcinoma (HCC) develops in the context of cirrhosis. A number of treatment modalities are now available to manage HCC including chemotherapy, (chemo)arterial embolisation, radiofrequency ablation, percutaneous alcohol ablation, and resection, as well as LT. All patients with HCC should be referred to a centre where these therapies are available to suit the individual patient's particular need.

Resection can be used for patients with non-cirrhotic HCC, dependent on stage and location of disease. However, for patients with cirrhosis, resection should only be considered in individuals with normal serum bilirubin (Child-Pugh class A, Table 1.2) and with hepatic venous pressure gradient (HVPG) < 10 mmHg. Long-term survival rates for such patients undergoing resection for HCC can exceed 70% at 5 years.

Most transplant centres use transplant selection criteria as defined by Mazzaferro relating to:

- size (single lesion < 5 cm);
- multiplicity (up to 3 lesions < 3 cm); and
- the absence of local or distant invasion;
- or variations of these.

Following transplantation, 5-year survival rates of over 70% are recorded. Nevertheless, because some patients with HCC outside those criteria may have a good post-LT outcome and some patients with a single small HCC have a poor outcome due to early and aggressive tumour recurrence, there are ongoing efforts to refine the selection criteria. Radiological size and number of tumours is a poor surrogate of tumour stage or biology.

Poor histological differentiation and the presence of macro- or microvascular invasion have repeatedly been found to be independent predictors of post-transplant outcome. Tumour biopsy has been proposed as a means of obtaining information on differentiation status but utility is limited by sampling error, concerns about tumour spread, heterogeneity of differentiation status within a single tumour, and because microvascular invasion is often only seen in a very small section of the tumour. Other criteria that might reflect tumour biology include tumour doubling time over a specific period, response to adjuvant therapy or downstaging, and level of α-fetoprotein. However, some authors have reported reduced survival rates using extended HCC selection criteria; hence these are not yet recommended in many centres.

Referral summary

- Referral to a transplant centre will need to take all these factors into account as well as the particular transplant selection criteria used within the transplant centre.
- That is best achieved by referral of all patients identified as having a focal liver lesion with the characteristics of HCC and within criteria for LT to a transplant centre multidisciplinary team meeting in order that, where appropriate, LT is considered.
- When a liver lesion(s) characteristic of HCC (arterial hypervascularity and portal venous phase washout) is detected, referral to a liver centre should be considered for all patients who are otherwise appropriate candidates.
- A full range of treatment modalities including resection and other adjuvant therapies should be considered as well as LT.
- Adjuvant pre-transplant therapy should be considered, particularly if waiting times are lengthy.

Chronic liver disease: natural history

In patients with established chronic liver disease and cirrhosis the mortality risk relates to the development of either superimposed HCC or to complications of portal hypertension. It is possible to differentiate four clinical stages of cirrhosis, based on the presence or absence of complications related to portal hypertension (Box 1.1).

Identifying the stage of an individual patient's progression will aid timely referral to a transplant centre. Late referral resulting in transplantation when there is severe liver failure or renal impairment is associated with worse outcomes.

Box 1.1 Clinical stages of progression of cirrhosis

- Stage 1 – cirrhosis; no varices, ascites; annual mortality 1%
- Stage 2 – cirrhosis; varices, no haemorrhage, no ascites; annual mortality 3.4%
- Stage 3 – cirrhosis with decompensation (ascites); annual mortality 20%
- Stage 4 – cirrhosis with decompensation (variceal haemorrhage) annual mortality >50%

(Source: D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 18 studies. J Hepatology. 2010;44:217–31.)

Chronic liver disease: prognostic scoring systems

In order to identify the optimum timing for transfer, the use of scores accurately predicting short-term mortality has been proposed. In the management of individual patients with cirrhosis it is clearly important to accurately define anticipated medium- and long-term outcomes.

- The Child-Pugh score (CPS) uses a combination of objective and subjective variables (Table 1.2), has moderately good predictive accuracy, but also well-documented limitations. These include arbitrary categorisation of clinical parameters such as ascites and encephalopathy, laboratory variability in measurement of prothrombin time, and a ceiling and floor effect for a number of the variables.
- The model for end-stage liver disease (MELD) score uses only objective continuous variables and has gained acceptance as a useful predictive tool in a number of different clinical contexts. Nevertheless, the evidence for the superiority of MELD over CPS for short-term prognostication in patients with severe liver disease is still a matter of debate.
- A number of refinements to MELD have included recalibration of the three laboratory parameters (refit MELD), addition of serum sodium to

Table 1.2 Child-Pugh score

Points	1	2	3
Albumin (g/L)	>35	28–35	<28
Bilirubin (μmol/L)	<34	34–50	>50
Prothrombin time (s)	<4	4–6	>6
Ascites	None	Mild	Moderate
Encephalopathy	None	Grade 1–2	Grade 3–4

Score 5–6 = class A, 7–9 class B, 10–15 class C.

the score (MELD-Na) and recalculation of a score on new cohorts of patients awaiting transplantation (UK end-stage liver disease score – UKELD). UKELD was derived from a cohort of UK patients listed for transplantation and was found to be more accurate than MELD in that population. While the variables scored in UKELD are similar to those in MELD-Na, the coefficient weightings are different.

With all these scoring systems there is the possibility of inter-laboratory differences between assays (INR), variations in serum creatinine related to gender, ethnicity and diuretic use, as well as changes in serum sodium with diuretics.

Referral summary

- In patients with chronic liver disease, the development of decompensated cirrhosis (ascites, variceal haemorrhage, spontaneous bacterial peritonitis and encephalopathy) should raise the need for transplantation and patients should be discussed with a transplant centre.
- The use of prognostic scores in all patients with chronic liver disease may aid prediction of short-term prognosis and timing of referral to a transplant centre.
- A score predicting worse outcome without transplantation at 1 year compared to predicted survival with transplantation should initiate referral; Child-Pugh ≥ 8, MELD ≥ 10, UKELD ≥ 49.
- Physicians involved in the care of patients with cirrhosis should inform their patients early of the need to improve any modifiable risk factors.

Chronic biliary diseases: primary biliary cirrhosis, sclerosing cholangitis

Most prognostic scores for patients with cirrhosis are independent of the aetiology of the chronic liver disease. Disease-specific scores have been developed but have not been widely introduced. Some clinical symptoms, particularly in cholestatic disease, are important. In patients with primary biliary cirrhosis, severe osteopenia and intractable pruritus should prompt consideration of transfer to a transplant centre. Similarly, patients with recurrent bacterial cholangitis in (primary) sclerosing cholangitis (PSC) may experience intermittent and severe episodes of decompensation punctuated by periods with well-maintained liver blood tests. Prophylactic oral antibiotics are commonly ineffective. Blood tests may underestimate the mortality risk without transplantation, therefore recurrent cholangitis is a further indication for transfer to a transplant centre. The presence of a cholangiocarcinoma in patients with sclerosing cholangitis is currently a contraindication to LT in most centres.

Referral summary

- In cases with chronic biliary disease consider transplantation: as judged by prognostic scores in line with locally agreed criteria for chronic liver disease; for intractable pruritus not manageable by any medication; in a patient with recurrent, debilitating, non-traumatic bone fractures; in the presence of recurrent, refractory bacterial cholangitis in a patient with extensive PSC.
- Do not refer patients with cholangiocarcinoma.

Diuretic-resistant/intolerant ascites and chronic hepatic encephalopathy

The natural history of cirrhosis demonstrates that within 10 years of diagnosis 30–50% of patients with cirrhosis will develop ascites. The prognosis for a patient once they have developed ascites is significantly worse than in patients with compensated cirrhosis, with a 40% 2-year mortality, and therefore referral for consideration of LT should be made when ascites develops. Refractory ascites unresponsive to diuretic treatment (DRA) or which recurs rapidly after therapeutic paracentesis is associated with a 50% 1-year survival rate. Patients may also progress to hepatorenal syndrome which carries very poor prognosis and should stimulate urgent referral to a transplant centre.

The management of DRA may involve recurrent paracentesis, insertion of TIPS shunt or LT. Although successful in up to 70% of patients and with advantages over recurrent paracentesis, there remains controversy as to whether mortality is improved by TIPS shunt, or whether progression to hepatorenal syndrome is prevented. Recent meta-analyses have demonstrated some survival advantage.

Chronic hepatic encephalopathy (HE) in the context of chronic liver disease is associated with a poor prognosis. Intermittent HE requiring hospital admission may disproportionately impact survival over and above that predicted by MELD and may rapidly respond to LT.

Referral summary

- Patients with cirrhosis who develop diuretic-refractory or diuretic-intolerant ascites should be referred rapidly for consideration of LT.
- Patients with type 1 hepatorenal syndrome should have expedited referral to a transplant centre.
- Patients with chronic HE or repeated admissions due to recurrent HE refractory to optimal medical management should be referred for consideration of LT.

Hepato-pulmonary syndrome

Hepato-pulmonary syndrome (HPS) comprises the presence of arterial deoxygenation, pulmonary vasodilatation and chronic liver disease. Given the importance of a diagnosis of HPS, patients should be screened by pulse oximetry, with threshold oxygen saturations of < 96% being a cost-effective cut-off for further investigation. Further evaluation for the presence and severity of HPS includes arterial blood gases, transthoracic echocardiography and estimation of the shunt fraction through a technetium-labelled macro-aggregated albumin (MAA) scan.

Because the median survival of a patient with severe HPS is less than 12 months, it is accepted as an indication for listing for LT. The severity of HPS is, however, a significant determinant of post-transplant survival, with the presence of an arterial oxygen concentration of ≤ 50 mmHg, or a shunt fraction > 20% strongly predictive of postoperative mortality. Hence certain patients may be deemed too high risk for LT simply based on the severity of HPS.

Referral summary

- Patients with hepato-pulmonary syndrome, irrespective of the severity of their chronic liver disease, should be referred for consideration of LT.

Porto-pulmonary hypertension

Porto-pulmonary hypertension (PPH) may occur in up to 4% of patients with cirrhosis and is diagnosed when mean pulmonary artery pressure (mPAP) is ≥ 25 mmHg, with an elevated pulmonary vascular resistance (>240 dyn/s/cm) and a normal pulmonary capillary wedge pressure (<15 mmHg). PPH may be asymptomatic or may present with non-specific symptoms such as fatigue, pre-syncope, palpitations, exertional breathlessness and orthopnoea. Clinician awareness is important. Patients should undergo transthoracic Doppler echocardiography and, where indicated, right heart catheterisation to assess mPAP and pulmonary vascular resistance.

A raised mPAP is known to have a negative impact on prognosis in cirrhosis and hence LT is a consideration. The presence of mild PPH (mPAP 25–34 mmHg) and moderate PPH (mPAP 35–44 mmHg) is not associated with worse outcomes after transplantation, but patients with severe disease (mPAP ≥ 45 mmHg) are usually excluded from selection due to adverse outcomes. PPH may improve slowly after LT although it may be slow.

Referral summary

- Patients undergoing transplant evaluation should be screened for PPH.
- Patients with porto-pulmonary hypertension should be discussed with a transplant centre regarding their suitability for LT.
- In patients found to have severe porto-pulmonary hypertension (mPAP ≥ 45 mmHg) LT is currently contraindicated but should be discussed with a transplant centre and in parallel with referral to a specialist in pulmonary hypertension in order to attempt drug therapy for PPH.

Patients who are human immunodeficiency virus carriers

Whereas the presence of HIV infection was previously regarded as a relative contraindication to LT, the current change in natural history related to antiretroviral therapy and the possibility of long-term control of viral replication has significantly changed the outlook. Liver disease is an increasingly important cause of morbidity and mortality in patients with HIV who have HBV or HCV coinfection. There is evidence that the rate of progression from initial decompensation to death is accelerated in HIV-coinfected patients. Following transplantation, coinfected HIV and HCV carriers have a slightly worse outcome compared to HCV patients. Undetectable HIV viral load and normal CD4 counts are important in the selection of candidates.

Referral summary

- HIV-positive patients with cirrhosis should be referred early for transplant assessment, and certainly after the first decompensation.
- Eligibility for transplantation should be assessed at a transplant centre experienced in the management of HIV.
- There are specific issues that may impact on decision-making regarding LT, including adequate control of viral replication, absence of viral resistance and immunosuppressant–antiviral drug interactions.

Other unusual indications

A number of rare conditions have also been considered for LT. The evidence of efficacy in these situations is often less impressive, but good survival has been recorded in many. Acute porphyrias, polycystic liver disease, primary hyperlipidaemia and primary familial amyloidoses are all appropriate indications for LT in rare circumstances where all other therapies have failed.

In carefully selected cases LT for rarer tumours such as hepatic epithelioid haemangioendothelioma and neuroendocrine tumours has been performed with good results.

Combined liver and kidney transplantation can be considered in the presence of simultaneous liver and kidney failure or for certain metabolic disorders such as primary oxalosis. All such cases require early and careful discussion with a transplant centre before transfer.

Specific medical surgical and psychosocial issues

Early referral of patients to transplant centres has the additional benefit that an assessment of an individual's comorbidities can be made. Factors that may be partially or completely reversible may be identified and treatment or modification of these factors may impact on suitability for LT and long-term survival. Such factors include:

- adequacy of control of diabetes mellitus;
- risk factors for cardiovascular and respiratory disease;
- other issues such as smoking, illicit drug use, obesity and alcohol use.

Obesity

Minor degrees of obesity are common in patients with cirrhosis, not just in patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. Following LT, morbidity and postoperative complications are increased with elevated body mass index (BMI) but the impact on survival is minimal except in morbidly obese patients (BMI > 40).

Cigarette smoking

Cigarette smoking is associated with adverse post-transplant outcomes related to an increased risk of hepatic artery thrombosis, cardiac disease and malignancy. Many centres require patients to enroll in smoking abstinence programmes before being accepted onto a transplant list.

Substance misuse

In many centres assessment and management of substance misuse represents a major challenge in potential transplant candidates. All patients must be given access to a substance misuse treatment programme. Current ongoing use of illicit or non-prescribed substances, non-compliance with treatment or failure to comply with assessment constitute contraindications to listing for LT. Stable methadone use is not a contraindication to LT, although postoperative complications are more common relating to pain control.

Summary

- Ongoing illicit drug or alcohol use, non-compliance with treatment or failure to comply with assessment is considered a contraindication to LT.
- Stable methadone use is not a contraindication but patients must be counselled about complexities in postoperative analgesia.
- Any patient with chronic liver disease using illicit drugs or abusing alcohol should be advised that ongoing substance misuse may preclude LT, should this be required in the future.
- Where appropriate, referral to the local substance misuse service must take place and continuing engagement demonstrated.

Alcohol

Alcohol-related liver disease is a major cause of liver mortality. Liver transplantation in abstinent patients with inactive alcoholic liver disease (ALD) is well accepted and the survival rates in the UK and elsewhere are excellent. Rejection, graft failure and the need for retransplantation are less common in patients with ALD compared with patients transplanted for other conditions, although they may experience an increased incidence of pharyngeal, esophageal or gastric malignancies late after transplantation.

Assessing the prospect for abstinence in patients with prior alcohol use is important. Currently a period of abstinence prior to transplantation is required in many transplant centres, in order to allow time for spontaneous recovery of liver function and thereby avoid unnecessary LT, rather than as a perceived predictor of long-term sobriety. Although the duration of abstinence prior to transplantation has some predictive value for sobriety, there is little evidence to support a rigid 6-month rule. Not all studies have demonstrated that the duration of abstinence is inversely a strong predictor of recidivism, and other factors including psychiatric comorbidities, social support networks, poly-substance misuse and age at onset of abuse are also critical. Some countries, for example the UK and France, have moved away from a 6-month rule to a comprehensive psychosocial assessment. Assessment is complex and best undertaken within multidisciplinary teams. Concerns about potential recidivism should not be a barrier to referral to a transplant centre.

In contrast, severe acute alcoholic hepatitis (SAAH), which carries a significant mortality, has not been an indication for liver transplantation in many countries. Despite that, retrospective series and a recent prospective study from France of transplantation in highly selected cases with SAAH have reported encouraging results. Rates of resumption of alcohol use were similar to those reported in other series of patients following transplantation for alcoholic liver disease.

Summary

- All patients who are potential transplant candidates and have consumed alcohol to excess must be assessed by multidisciplinary teams expert in the management of addictive behaviours.
- A full psychosocial assessment must be undertaken in patients with alcohol-related liver damage, examining all factors considered predictive of recidivism. This is best undertaken by a transplant centre.
- Patients with recurrent decompensated ALD in the context of ongoing or recurrent alcohol consumption are not appropriate referrals for LT.

Age

In Europe 20% of patients undergoing LT are more than 60 years old (www.eltr.org). Older patients have reduced long-term survival after transplantation related to frequency of diabetes mellitus, renal impairment, HCV carriage and a higher risk of late post-transplant malignancy. Despite that, there are no specific age limits to LT. The presence of comorbidities including diabetes, cardiovascular and respiratory diseases that may increase with age will need to be carefully assessed.

Compliance

Psychosocial problems are some of the hardest to assess and their impact on the need for referral to a transplant centre must not be underestimated. Psychiatric disorders must be adequately controlled such that they will not impact on compliance with medication and medical advice. In those circumstances patients may need substantial support and counselling, which can be particularly challenging where there are other features including low educational attainment, mental retardation, intermittent encephalopathy or when potential candidates are prisoners.

Summary

- Potential transplant candidates should be able to demonstrate reasonable compliance with medication and medical advice.
- Transplant teams and referral centres should make every effort to address issues of compliance and factors that impact on compliance, before assessment for LT.

Further reading

AASLD Practice Guidelines 2010 – Management of Hepatocellular Carcinoma. www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf.

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