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Indication and assessment for liver transplantation

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Liver transplantation provides effective therapy for most forms of acute and chronic liver failure – one-year survival rates exceed 90%[1] – and the indications continue to expand. In general terms, the indications for liver transplantation are objective evidence of liver failure and subjective criteria such as poor quality of life due to liver disease and occasionally rare metabolic defects.

Chronic liver disease

In chronic liver disease the most important aspect of patient selection is timing. Transplantation should improve both quality and quantity of life. The procedure is optimally carried out when the patient is well enough to withstand the procedure, but ill enough to warrant it (ie predicted survival is about 1–2 years without a transplant).

Assessment for transplantation in chronic liver disease is difficult. Objective and subjective measures are used. The Child-Pugh classification[2] (Table 1) allows objective assessment of a patient's functional liver status and in the USA forms the basis for the criteria required to list patients. Those with Childs C grade have a 58%, 21% and 0% one-year, five-year and 10-year survival, respectively.

Subjective measures of liver disease may be more difficult to assess. Tools are available to document quality of life[3], and a full psychosocial assessment should be carried out.

Cholestatic liver disease

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a declining indication for liver transplantation, but still accounted for 7.8% of liver transplants in Europe in 1998–2000[1]. The disease has three stages:

- an initial asymptomatic stage
- a symptomatic stage with worsening cholestasis and declining synthetic function (falling albumin and increasing prothrombin time)
- a decompensating stage with severe jaundice and evidence of portal hypertension.

The natural history of PBC is well defined. Various prognostic models have been designed. The most commonly used is the Mayo Clinic model[4]; this has

Key Points

There are objective and subjective criteria for transplantation

Disease-specific criteria exist for different conditions

Certain indications are common to all conditions, for example:
- failing synthetic function (serum albumin <25 g/l)
- complications of portal hypertension
- intolerable quality of life

Discussion/referral should occur prior to end-stage disease

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allowed prediction of estimated survival of PBC patients with and without transplantation.

Bilirubin may be used as an indicator for transplantation. Serum bilirubin levels of 100 µmol/l and 150 µmol/l give median survivals of 24 months and 17 months, respectively. Treatment with ursodeoxycholic acid has meant that patients are less likely to be transplanted as a result of their serum bilirubin, but more because of resistant ascites, other complications of portal hypertension (eg variceal bleed) or declining synthetic function. Occasionally, patients with PBC are transplanted because of intractable pruritus or severe lethargy.

Survival for PBC after transplantation is 80–90% at 10 years, with a low risk (<10%) of symptomatic PBC recurrence. Patients should be referred for transplantation if their expected survival is less than two years, but before they begin to decompensate rapidly or subjective features such as lethargy or pruritus make their quality of life intolerable.

Primary sclerosing cholangitis

Models exist for the prognosis of primary sclerosing cholangitis (PSC) and actuarial survival post transplant, using these models is 89% at five years, compared with 31% in medically managed patients[5]. The variables used to predict survival are serum bilirubin, haemoglobin, histological state on liver biopsy, age and presence of inflammatory bowel disease.

The indications for liver transplantation in patients with PSC include:

- severe jaundice (bilirubin >100 µmol/l)
- complications arising from portal hypertension, and
- poor quality of life.

There is a high rate of cholangiocarcinoma, with some studies suggesting a prevalence of 30% at 10 years. Undiagnosed cholangiocarcinoma is found in 8–18% of explanted livers, although incidental cholangiocarcinoma, either microscopic or smaller than 1 cm, does not necessarily affect prognosis.

Table 1. Childs grading of severity in chronic liver disease with Pugh's 1973 modifications.

Criteria assessed	Points scored for increasing abnormality		
	1	2	3
Encephalopathy grade	None	I–II	III–IV
Ascites	Absent	Slight	Moderate
Serum bilirubin (µmol/l):	<35	35–50	>50
In PBC	<70	70–170	>170
Serum albumin (g/l)	>35	35–28	<28
Prothrombin time (prolongation in sec):	1–4	4–10	>10
Total score	<6 A	7–9 B	>10 C

PBC = primary biliary cirrhosis.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) usually carries a good prognosis, with 93% five-year survival. Several features suggest a bad prognosis, such as onset in childhood, type II disease (liver-kidney microsomal antibody (LKM)-positive) and failure to respond to immunosuppressive treatment (associated with a 69% mortality at four years)[6].

Patients with AIH may present with acute liver failure. It may be possible to induce remission with appropriate immunosuppression, but this should be performed in a transplant centre so that, should treatment fail, emergency transplantation can be provided.

Transplantation for AIH has a good prognosis (80% five-year survival). Graft failure due to disease recurrence is rare. Referral for transplantation is usually for chronic liver failure when predicted survival is less than 1–2 years.

Alcoholic cirrhosis

Alcoholic cirrhosis is the second commonest indication for liver transplantation, accounting for 20% of European liver transplants.

When assessing a patient, non-dependent alcohol abuse should be differentiated from alcoholism. Most transplant programmes in the UK insist on a six-month abstinence period prior to transplantation and the signing of a 'no

alcohol contract' prior to listing. The six-month period of abstinence is important since some patients may recover during the time, thus negating the need for a transplant.

Assessment of patients with alcoholic liver disease includes investigations to rule out any comorbid alcohol-related illnesses such as cardiomyopathy, nutritional failure or nephropathy. In patients with alcoholic liver disease, cirrhosis is often a late development. The onset of ascites reduces median survival to 12 months, and the development of spontaneous bacterial peritonitis suggests a median survival of six months. Hepatocellular carcinoma (HCC) will be developed by 20% of patients with alcoholic cirrhosis, and 75% of patients will die from their liver disease.

Viral hepatitis

Hepatitis B

Hepatitis B is a common cause of cirrhosis worldwide, but less so in the UK. The outcome of transplantation for hepatitis B was universally poor in the early days of transplantation due to graft reinfection and the rapid onset of liver failure. It is mandatory that patients with end-stage hepatitis B virus (HBV) infection are rendered HBV DNA negative with antiviral agents such as lamivudine prior to transplantation. Recurrence of hepatitis B after transplantation is pre-

vented by administration of hepatitis B immunoglobulin.

Five-year survival for patients with compensated HBV cirrhosis (ie Childs A disease) is 85%, and for decompensated disease (Childs C) is between 14 and 35%[7]. Indications for transplantation in HBV are objective criteria of liver failure, with declining serum albumin usually the best early indicator. Concerns over graft reinfection mean that patients with subjective symptoms are managed medically.

Hepatitis C

Hepatitis C is the commonest indication for transplantation worldwide. Of those infected with hepatitis C, 80–90% of patients will become chronic carriers and 20% will later develop hepatitis C virus (HCV)-related cirrhosis, usually over longer than 20 years. Several risk factors are associated with more rapid progression of disease:

- male sex
- excess alcohol intake
- HBV co-infection, and
- route of transmission (blood products providing the highest risk).

Patients with Childs C disease should be considered for transplantation. Timing of transplantation is important because graft reinfection with HCV is universal and graft cirrhosis is reported in up to 20% of patients at five years[8] (although five-year survival is about 70%). Transplantation should be delayed until there is objective evidence of liver failure because accelerated cirrhosis may develop after transplantation.

Carcinoma

It was hoped that hepatic transplantation might cure many malignant diseases. Unfortunately, results have been disappointing and transplantation in malignancy is now restricted to HCC, some neuroendocrine tumours and a few other rarities.

HCC has a poor outcome. Median survival without treatment is around six months. Improvement in survival post-transplant for patients with HCC

has been achieved by tightening the criteria for transplantation: a single lesion of less than 5 cm or less than five lesions in total and no evidence of vascular or capsular invasion. Transplantation outside these guidelines should occur only as part of a clinical trial.

Metabolic indications

There are several metabolic indications for liver transplantation (Table 2). Wilson's disease can present both as chronic liver disease and as acute liver failure. In the acute situation, patients invariably die without liver transplantation. Genetic haemachromatosis is the commonest inherited genetic disorder in Northern Europe. If patients are diagnosed before cirrhosis has developed, iron depletion treatment (venesection) is

Table 2. Metabolic indications for liver transplantation.

- Wilson's disease
- genetic haemachromatosis
- alpha-1-antitrypsin
- oxalosis
- Crigler-Najjar syndrome
- familial amyloidosis
- hereditary tyrosinaemia
- urea cycle defects
- galactosaemia.

successful, but the outlook is not so good once cirrhosis has developed. Patients may decompensate or develop HCC, especially if alcohol misuse is a cofactor. Alpha-1-antitrypsin is another inherited disorder for which transplantation is indicated when a patient has decompensated cirrhosis. In this situation, the outlook is excellent and soon after transplant the patient expresses the alpha-1-antitrypsin phenotype of the donor organ.

Other indications

Many other indications exist for transplantation. Transplantation may be used as a rescue therapy in Budd-Chiari syndrome, but it is often technically challenging. Transplantation also has a role in structural disorders such as polycystic liver disease.

Acute liver failure

Aetiology is the most important variable predicting survival in acute liver failure. The commonest cause of acute liver failure in the UK is paracetamol toxicity followed by seronegative hepatitis, hepatitis B, drug reactions and hepatitis A. Seronegative hepatitis (non-A to non-E hepatitis) confers the least favourable outcome, drug-induced liver failure has an intermediate prognosis and paracetamol-induced failure the best[9]. Age is another predictor, with

Table 3. King's College Hospital criteria for transplantation in acute liver failure.

Paracetamol related	• pH <7.30 despite adequate fluid resuscitation (regardless of grade of encephalopathy)
	or
	• Prothrombin time >100 sec **and** creatinine >300 µmol/l **and** grade III or IV coma
Non-paracetamol related	• Prothrombin time >100 sec (regardless of grade of encephalopathy)
	or
	• Any three of the following (regardless of grade of encephalopathy) (a) aetiology: non-A non-B hepatitis, idiosyncratic drug reactions (b) age <10 or >40 years (c) jaundice to encephalopathy of >7 days (d) prothrombin time of >50 sec (e) serum bilirubin >300 µmol/l

extremes of age being associated with the worst outcomes.

The selection of patients for transplantation in acute liver failure is directed by the use of predictive models. The King's College criteria (Table 3), formulated following retrospective analysis of 588 patients with acute liver failure, are adhered to by transplant units in the UK. Several studies have validated these criteria. They have a high specificity and positive predictive value, but a low negative predictive value for a poor outcome. Fulfilling the criteria confers less than 10% chance of survival[10].

In acute liver failure it is vital that patients are referred for consideration for transplantation at an appropriate time – *before* their disease fulfills the King's College criteria. It is advisable that the management of any patient who has acute liver failure and is becoming encephalopathic, developing renal failure or has a rising international normalised ratio should be discussed with a transplant centre. Sometimes a matter of hours can mean the difference between life and death.

Contraindications

There are no absolute contraindications to liver transplantation. Many patients who previously would not have been transplanted can now be assessed and transplanted safely. However, some patients have conditions which confer high risks, including:

- extrahepatic organ failure
- extrahepatic malignancy
- severe extrahepatic infection
- AIDS and HIV positivity
- portal venous system thrombosis
- on-going substance misuse
- comorbidity (eg diabetes mellitus).

Chronological age is not a contraindication to transplantation, although transplantation in patients over the age of 65 requires careful consideration.

Conclusion

Liver transplantation is a relatively safe and successful treatment modality that can be employed in patients with acute and chronic liver disease. Optimal timing is extremely important. Objective measures of liver failure should be assessed, one of the most important of which is serum albumin especially in the non-jaundiced patient. A serum albumin of less than 25 g/l suggests a poor outlook. Serum albumin should not be overlooked since this is often the most subtle sign of liver failure. Subjective aspects should also be considered: quality of life and the ability to work and participate in society.

Careful consideration of these factors should be given to optimise the use of a scarce resource, whilst ensuring that patients with liver failure are not denied the opportunity of assessment for liver transplantation.

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