Liver transplantation

James W Ferguson

Abstract

Liver transplantation is a successful therapy for end-stage liver disease, hepatocellular carcinoma and acute liver failure. Early referral is essential to allow time for careful assessment. The patient's needs need to be balanced against the predicted outcome after transplantation. The calcineurin inhibitor tacrolimus is the mainstay of immunosuppression in liver transplantation. Outcomes after liver transplantation are excellent but patients do not have a normal quantity or quality of life compared with an age- and sex-matched population.

Keywords Acute liver failure; allocation; donation; liver transplantation; MRCP; mycophenolate; tacrolimus

Key points

- Refer early for liver transplantation
- Hepatocellular carcinoma is a common indication for transplantation and outcomes are good
- Acute liver failure should be primarily managed in tertiary liver centres that have access to liver transplantation

Introduction

Liver transplantation is a highly effective therapy for patients with acute or chronic liver disease. The number of indications is gradually growing, and outcomes continue to improve. New advances in surgical techniques have led to the development of living donation and the use of higher risk grafts. Despite this, waiting list mortality remains a problem because of the increasing burden of liver disease.

When to refer

There are a number of general considerations to take into account before referral:

- The patient should be sick enough to justify liver transplantation, and all other potential avenues of therapy ought to have been pursued.
- The patient should be fit enough to survive the procedure, able to comply with medication and not have significant co-morbidities that affect survival.

Early referral is important as this allows time for careful assessment and education of the patient and family. Furthermore, acceptance onto a transplant list does not equate with immediate transplantation, with many patients waiting >6 months for a graft.

Chronic liver disease

The advent of decompensation of cirrhosis (ascites, encephalopathy, spontaneous bacterial peritonitis) merits consideration for referral for liver transplantation. However, there are also a number of prognostic scoring systems that help clinicians to predict longer term outcome and therefore the need for grafting. These include the Model for End-stage Liver Disease (MELD), United Kingdom Model for End-stage Liver Disease (UKELD) and Child–Turcotte–Pugh scores (Tables 1 and 2).[1] A score that predicts a worse outcome without transplantation at 1 year than survival with transplantation (Child–Pugh ≥8, MELD ≥10 and UKELD ≥49) should lead to a referral.

Hepatocellular carcinoma (HCC)

Transplantation is an excellent therapy for selected patients with HCC as it potentially cures both the cancer and the underlying liver disease.[2] Selection remains a controversial topic, and many scoring systems have been proposed to help pick patients with the most favourable outcome. The most commonly used criteria are the Milan criteria, which suggest that transplantation is beneficial in patients with one lesion ≤5 cm in size, or ≤3 lesions each ≤3 cm in size.

Acute liver failure

Acute liver failure should be primarily managed in tertiary liver centres that have access to liver transplantation. In cases of paracetamol toxicity, patients should be referred if there is:

- evidence of pH <7.4
- elevated serum lactate >2.5 mmol/litre after fluid resuscitation
- a prolonged prothrombin time, renal impairment or encephalopathy.

In cases of non-paracetamol toxicity, refer the patient if there is:

- an international normalized ratio (INR) >1.5
- any encephalopathy
- a severe presentation of autoimmune hepatitis
- acute Wilson's disease.

Child–Turcotte–Pugh classification

Measure	1 point	2 points	3 points
Total bilirubin, micromol/litre (mg/dl)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8–3.5	<2.8
International normalized ratio	<1.7	<1.7–2.3	>2.3
Hepatic encephalopathy	None	Grade 1–2	Grade 3–4

Table 1

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MELD score

MELD = 3.78 × ln [serum bilirubin (mg/dl)]
+ 11.2 × ln [INR]
+ 9.57 × ln [serum creatinine (mg/dl)]
+ 6.43

If the patient has had renal replacement therapy twice within the previous 7 days, serum creatinine should be set at 4 mg/dl.

See https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/.

Table 2

Prognostic models exist that help the transplant team to identify individuals with a poor prognosis at the earliest moment. The most commonly used model is the King's College criteria developed in 1989 (Table 3); this has separate criteria for non-paracetamol and paracetamol aetiologies.[3]

Variant syndromes

A number of variant syndromes exist that benefit from liver transplantation, including:

- hepatopulmonary syndrome
- polycystic liver disease
- porphyria
- primary familial amyloidosis.

Donation and allocation

Donation

The majority of liver transplants in the UK are deceased heart-beating donor grafts. However, a significant proportion, up to a third in some centres, are grafts from donors after circulatory death, which carry a higher risk of primary non-function and biliary problems. However, new methods of organ perfusion are likely to change the types of graft that can be accepted and reduce complications from previously categorized high-risk grafts.

King's College criteria

The King's College criteria identify two groups of patients who have a poor prognosis with paracetamol-induced liver failure, those with:

- Arterial pH <7.3 (taken by sampling of blood from an artery)
- All three of INR >6.5, serum creatinine >300 micromol/litre and the presence of encephalopathy (grade 3 or 4)

In patients with non-acetaminophen acute liver failure, the following criteria have been identified as being associated with a poor prognosis:

- INR >6.5; *or*

Three of the following five criteria:

- Patient age <11 or >40 years
- Serum bilirubin >300 micromol/litre
- Time from onset of jaundice to the development of coma of >7 days
- INR >3.5
- Drug toxicity, regardless of whether it was the cause of the acute liver failure

Table 3

Living donation is the primary form of liver transplantation in many parts of the world where deceased donation is not culturally acceptable. Living related donation carries a 0.1–0.5% risk of mortality and a 15% risk of complications.

Allocation

Allocation of liver grafts is a complex process that aims to decide which patient should be offered treatment when there are limited resources. The needs of the patient must be balanced against the predicted outcome after transplantation.

The UK uses a model known as the Transplant Benefit Score, calculated using 21 recipient and seven donor factors. Livers are offered nationally to named patients predicted to gain the most survival benefit from being given the particular liver graft on offer. The USA uses a different model primarily based on need and the MELD scoring system.[4]

Important points about the surgical procedure

- Always read the operation note when evaluating a transplant recipient.
- The liver is usually implanted in the same place as the removed liver.
- The biliary anastomosis can be a straightforward join of the donor bile duct to the recipient bile duct or a hepaticojejunostomy (for diseased bile ducts and often in retransplantation). This is important as biliary intervention from endoscopic retrograde cholangiopancreatography can be very challenging in patients who have a hepaticojejunostomy.
- The hepatic arterial anastomosis is normally a donor-to-recipient arterial join but in some cases can be an arterial conduit.
- The donor portal vein is anastomosed to the recipient portal vein.
- The reconstruction of the hepatic outflow is most commonly done using a modified piggy-back technique (which allows removal of the liver without removing a portion of the cava) but can be a classical piggy-back or caval replacement.

Outcomes

Outcomes after liver transplantation are excellent but patients do not have a normal quantity or quality of life compared with an age- and sex-matched population. The outcome of the graft is affected by rejection, technical issues and recurrent disease (primary sclerosing cholangitis, primary biliary cholangitis, alcohol, non-alcoholic fatty liver disease, HCC). The outcome for patients is predominantly affected by complications associated with long-term use of immunosuppression. These include renal impairment, malignancy, propensity to infection and cardiovascular disease.

Immunosuppression

Liver transplantation is only an effective procedure because of effective immunosuppression. Grafting of a liver leads to a T-cell-mediated response causing graft injury if left untreated. Most centres use a regimen based around tacrolimus[5] with or without

an antimetabolite (azathioprine, mycophenolate) and a short course of corticosteroids in the early postoperative period.

Tacrolimus is a calcineurin inhibitor and is the mainstay of immunosuppression in liver transplantation. Its main adverse effects are nephrotoxicity, diabetes mellitus, hypertension and neurotoxicity.

Mycophenolate often causes gastrointestinal adverse effects including nausea, diarrhoea and vomiting. It is teratogenic and therefore contraindicated in patients considering pregnancy. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 54-year-old man presented with symptoms and signs of chronic liver disease related to alcohol.

What is the best scoring system to predict outcome in 1 year?

A. Child–Pugh score
B. United Kingdom Model for End-stage Liver Disease (UKELD)
C. Model for End-stage Liver Disease (MELD)
D. King's Acute Liver failure score
E. Milan criteria

Question 2

A 24-year-old woman presented with symptoms and signs of acute liver failure after a paracetemol overdose.

Which of the following criteria have been associated with a poor prognosis?

A. Amount of paracetemol ingested
B. INR> 6.5
C. Low serum potassium
D. Low serum phosphate
E. Low serum lactate

Question 3

A 32-year-old woman presented for review following liver transplantation for primary biliary cholangitis. She was commenced on tacrolimus.

What common unwanted effect of this drug should be discussed with her?

A. Renal failure
B. Poor wound healing
C. Diarrhoea
D. Teratogenicity
E. Neutropenia