



Liver transplants: great advances but still great need

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Pharmaceutical background

Liver transplantation was developed in the US during the mid-1950s with initial animal experimentation. Cyclosporin was discovered as a natural fungal by-product by Jean-Francois Borel in 1972. Roy Calne then demonstrated that cyclosporin not only improved graft survival in animals, but also could cause nephrotoxicity. Further studies helped to develop safe combination regimens limiting side effects of immunosuppressive drugs by using a cocktail approach. Cyclosporin has been replaced in recent years by tacrolimus whilst mycophenolate mofetil has largely replaced azathioprine. Monoclonal antibodies can be given either at induction or the initial post-operative period as part of a calcineurin inhibitor-sparing regimen in patients with established chronic kidney

disease. By and large, the liver is a relatively immunotolerant organ and does not require large amounts of immunosuppression.

Increasing the pool of liver donors ABO incompatible donors

The organ shortage continues. The number of people awaiting organ transplantation greatly exceeds the number of organs available. The criteria for donor livers have been relaxed slightly to include non-heart-beating donors, due to the pressure for donor organs. There is increasing evidence that patients with fulminant hepatic failure can receive a donor liver, not matched to their blood group, without significant complication. ABO incompatible grafts are often used when the clinical situation requires urgent transplantation.

Living related donors and auxiliary partial transplants

A significant minority of patients can be treated by splitting the donor liver into right and left lobe and performing a partial liver transplant using one half. The quality of the donor liver and the clinical condition of the recipient are vital determinants of the risk associated with partial transplantation. The long-term benefits are a life without immunosuppression once the native liver has recovered.

Living related liver donation uses the left half of the liver, donated by a family member, often from a parent to a child, due to the lower morbidity of left lobe resections. It is also the smaller of the two lobes and a suitable size for most children.

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Indications for liver transplantation in patients with acute liver failure

Patients with acute liver failure develop multi-organ and metabolic failure; the degree to which this extends affects the outcome. King's College Hospital London, UK, was the first centre to devise a system of early indices of prognosis in patients with acute liver failure who may require liver transplantation.

Introduction

There are around 400 cases of acute liver failure (ALF) in the UK annually [1]. It is a multi-system disorder, which occurs after an acute insult to the liver leading to the development of coagulopathy and encephalopathy over a short period of time, in a patient who has no preceding liver disease. The severity is determined by the underlying aetiology, patient's age and duration of time over which the disease evolves. ALF can be classified as hyperacute, acute and subacute, which relates to the time course of the disease, within 7 days, 8–28 days and more than 28 days respectively describ-

ing the period of symptoms to onset of encephalopathy. In Denmark, the UK and the US, the commonest cause is paracetamol hepatotoxicity. In other countries hepatitis B, serologically-negative and drug-induced hepatitis are the commonest causes. 'Ecstasy'-induced hepatotoxicity is increasingly encountered in young patients. Mortality for ALF exceeded 80% until orthotopic ('in the normal position') liver transplantation became available, and is mostly related to the complication of cerebral oedema or progressive multiple organ failure and vasopressor-resistant shock in association with sepsis [2].

Diagnosis and prognosis

Spontaneous recovery in ALF ranges between 10–90% and is largely determined by the underlying pathology. Diagnosis of the underlying aetiology is consequently both important for prognosis and management. A number of blood investigations can be performed to detect hepatocellular loss and dysfunction of both hepatic metabolism and synthesis. These include aspartate and alanine transaminases, bilirubin, prothrombin time, lactate and blood glucose indicating hypoglycaemia. Specific liver disease may be suggested by specific patterns of liver dysfunction – elevated

alkaline phosphatase may suggest an infiltrative process whilst low levels of alkaline phosphatase may suggest a diagnosis of Wilson's disease. More diagnostically specific tests include viral serology for hepatic viruses, plasma ceruloplasmin and urinary copper concentration for Wilson's disease and radiological imaging to evaluate the liver, spleen and vascular patency.

Clinical criteria predicting prognosis in patients with ALF were first described at King's College Hospital, London, UK. A

retrospective analysis of patients with ALF medically managed between 1973 and 1985 was performed to identify prognostically significant clinical factors. The value of these factors was then assessed with the subsequent development of the King's criteria, which now assist in the identification of patients who will benefit from liver transplantation [3].

Table 1 below stems from this early work and forms the basis for establishing risk of death without transplantation.

Because patients may deteriorate rapidly, urgent transfer to a centre with experience and expertise in managing patients with ALF will secure the best possible outcomes for these patients. Once in a specialised centre, patients are stratified for transplantation consideration according to blood group and time on the super urgent list.

These combinations of cause and signs/symptoms define those most at risk of dying from acute liver failure. Survival is estimated to be <20% without 'super urgent' transplantation.

Other criteria have also been developed to assist in the accurate determination of prognosis in other groups of patients. Most commonly used would be those of the Clichy group for non-paracetamol, or the BiLE score. In paracetamol-related disease P04 and alpha fetoprotein levels may also be used. In the US it has been suggested that liver volume may be used to determine prognosis, with decreased volume of <1,000 mL carrying a poor prognosis.

Patients will often develop clinical complications, which can preclude transplantation while waiting for a transplant. Therefore, the timing of referral to a specialist liver centre is of vital importance to patient care. There are several organ-specific clinical factors, which can be used to help determine who should be transferred to a specialist centre (see Table 2). These also stem from those factors known to determine specific complications and prognosis.

Paracetamol-induced hepatotoxicity often follows a relatively predictable time course of events unless there has been a staggered overdose. Coagulation abnormalities normally peak at 72 hours post ingestion whilst encephalopathy may not peak until day 5, although it may occur earlier. The criteria for referral remain the same for this condition as for other causes of ALF, but include severe thrombocytopenia and international normalised ratio (INR) or prothrombin time changes

Table 1: Greatest risk of death can be defined in these terms

Category	Aetiology	Indication for super urgent listing
1	Paracetamol poisoning	pH <7.25 more than 24 hours after overdose despite aggressive fluid resuscitation
2	Paracetamol poisoning	Co-existing prothrombin time >100 seconds or INR >6.5, and serum creatinine >300 mmol/L or anuria, and grade 3–4 encephalopathy
3	Paracetamol poisoning	Serum lactate more than 24 hours after overdose >3.5 mmol/L on admission or >3.0 mmol/L after aggressive fluid resuscitation
4	Paracetamol poisoning	Two of the three criteria from category 2 with clinical evidence of deterioration (e.g. increased intrahepatic cholestasis, fraction of inspired oxygen (FIO ₂) >50%, increasing inotropic requirements) in the absence of clinical sepsis
5	Seronegative hepatitis, hepatitis A, hepatitis B, or an idiosyncratic drug reaction	Prothrombin time >100 seconds or INR >6.5 and any grade of encephalopathy
6	Seronegative hepatitis, hepatitis A, hepatitis B, or an idiosyncratic drug reaction	Any grade of encephalopathy, and any three from the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time >7 days, serum bilirubin >300 mmol/L, prothrombin time >50 seconds or INR >3.5
7	Acute presentation of Wilson's disease, or Budd–Chiari syndrome	A combination of coagulopathy and any grade of encephalopathy
8	Hepatic artery thrombosis on days 0–21 after liver transplantation	
9	Early graft dysfunction on days 0–7 after liver transplantation	Two of the following: aspartate transaminase AST ≥10,000 IU/l, INR ≥3, serum lactate ≥3 mmol/L, absence of bile production
10	Any patient who has been a live liver donor	Severe liver failure within four weeks of the donor operation

INR: international normalised ratio
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related to the time of initial ingestion of the overdose (see Table 3) [5].

Indication for transplantation referral after paracetamol ingestion depends on both coagulation abnormality and time since ingestion.

Patients with ALF are best managed in a critical care environment once they start developing organ dysfunction. Transfer of patients to a tertiary centre requires coordination and consideration of the possible rate of deterioration that may occur. Some patients may require intubation for safety of transfer and all patients should be transferred accompanied by members of staff who are capable of dealing with rapid changes in physiology.

Upon arrival at the specialist intensive care unit critically ill patients with ALF are thoroughly re-evaluated, and supportive organ therapies continued. A multidisciplinary approach drawing on the experience and expertise of liver intensivists (intensive care physicians working on a specialist liver unit), hepatologists and transplant surgeons is crucial. All help determine an optimal treatment plan, including the key decision of listing for transplantation. There are often significant comorbidities which, either in isolation or in combination with

social and mental health issues, makes this decision difficult. A detailed collateral history in conjunction with further investigations to evaluate cardiovascular reserve and an ongoing endeavour to make a diagnosis, if not already established, is important. Once criteria are met and the patient is placed on the super urgent list for transplantation there is an ongoing requirement for regular re-evaluation of the suitability for transplantation. This will normally be undertaken at least twice a day and if/when a liver is offered.

Much of the work up that is available for a patient with chronic liver disease cannot be undertaken in ALF. Patients will need assessment of their cardio-respiratory status, either by direct measurement through invasive monitoring and/or echocardiography. The presence of acute renal failure is not a contraindication and does not necessitate the need for concomitant renal transplantation. Cerebral dysfunction is managed clinically with deep levels of encephalopathy (grade 3/4 coma) requiring intubation and ventilation. The decision to proceed to intracranial pressure monitoring is based on risk assessment (pupillary abnormalities, age, aetiology, and need for vasopressors, renal failure, and hyponatraemia). Radiological imaging of the brain does not define the risk of cerebral oedema

and intracranial hypertension but may be undertaken in patients in whom pupillary abnormalities are observed where there is concern about a focal defect such as an intracranial bleed. Liver imaging is normally undertaken with ultrasound alone, especially in the hyperacute groups, although in some instances axial imaging may be required. Similarly if there is concern regarding aetiology there is a requirement to exclude chronic liver disease or to exclude malignancy then a transjugular biopsy may be required.

Once listed the decision not to proceed to transplantation is normally undertaken on the basis of clinical deterioration. There are no absolute criteria in this regard and the decision in relation to an individual case must take into context comorbidity and dynamic data.

The presence of fixed dilated pupils unresponsive to medical therapies for a period of more than several hours is likely to result in withdrawal from the active transplant list due to concerns regarding irreversible brain injury. In the UK decisions are not made on the basis of cerebral perfusion pressure. Culture-positive sepsis is a relative contraindication and most centres would require at least 24 hours of appropriate antibiotic therapy. Trends are more important with regard to cardio-respiratory factors than absolute values although rapidly rising vasopressor requirements in excess of 1.5 µg/kg/min or a falling cardiac index (<2.5–3 L/min/m²) or deteriorating gas exchange unresponsive to recruitment and appropriate ventilatory technique may preclude transplantation. It is these decisions that require the input of an experienced multidisciplinary team.

ABO-incompatible liver transplants have been performed in critically ill patients who require an urgent liver transplant. Much debate about the potential and realised complications associated with ABO-incompatible grafts has suggested that there is an increase of

Table 2: Referral guide based on clinical factors

Organ	Sequelae	Measure	Level to refer
Brain	Encephalopathy	Modified Parson Smith (Grade 1–4)	Grade 1
Kidney	Acute kidney injury	Serum creatinine (acute kidney injury staging Stage 1–3)	Creatinine >130µmol/L Stage 1
Liver	Coagulopathy	INR or prothrombin time	>2 or >30 seconds
	Gluconeogenesis	Bilirubin Hypoglycaemia	>150µmol/L <3.5µmol/L
Metabolic	Sodium	Hyponatraemia	Na+ <135µmol/L

Table 3: Referral guide based on blood clotting

Time	48 hours	72 hours	96 hours
INR or prothrombin time	>3 or >50 seconds	>4.5 or >75 seconds	>6 or >100 seconds
INR: international normalised ratio			

incidence of graft failure, biliary complications and arterial thrombosis [6]. Despite this there is growing evidence that it is possible to safely transplant patients using cadaveric ABO-incompatible grafts.

There is growing interest in auxiliary, partial, liver transplantation and extracorporeal liver supportive therapies as an alternative to whole liver grafts. As for NHBD liver transplantation there needs to be careful selection of patients and grafts that would be suitable for use as an auxiliary graft. The recipient considerations fall squarely on the failing damaged liver in ALF driving haemodynamic instability and the neurological insult of cerebral oedema. The improvement in haemodynamics and cerebral oedema seen after a whole liver transplant in conjunction with explanting the native damaged liver may not be realised with auxiliary grafts. They are also technically more difficult and associated with more complication, especially biliary leak. The graft needs to be of

an appropriate size for the patient to provide sufficient functioning liver parenchyma to improve the clinical condition.

Summary

Liver transplantation is the best therapeutic option for patients with acute liver failure and multi-organ and metabolic failure if the disease process has not extended beyond the point of benefit. Donor liver resources are scarce, compounding the difficulty for those endeavouring to ensure the right individual decision is reached regarding the risks and benefits of liver transplantation. Extracorporeal therapies continue to be researched to provide an alternative, but this has as yet to be realised.

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Medication Safety

Ambiguous drug doses on discharge lists

Hospitals may need to improve the way medication lists are given to patients and other providers when discharging patients from the hospital. Using a computer-generated list or copying from the medication administration records (MARs) might lead others to confuse drug doses if different strengths of the medication are available. Due to cost containment and space limitations in automated dispensing cabinets, some hospital pharmacies stock a minimum variety of dosage strengths for a drug. Thus, nurses are directed to use multiple dosage units or half tablets to administer the prescribed dose. For example, a hospital may stock 100 mg tablets of Seroquel (quetiapine fumarate) but not the 200 mg, 300 mg, and 400 mg tablets. A patient who needs a 200 mg dose would be given two tablets of the 100 mg strength. MARs fre-

quently list the number of tablets to give along with the dose, as in the following example: 'Seroquel 100 mg, 2 tablets twice daily'. Although not recommended, the MAR may even just list '2 tablets = 200 mg'. Healthcare providers in outpatient settings may find this confusing, making the MAR a less-than-ideal document from which to prepare a discharge medication summary. One hospital recently reported that a patient discharged to a long-term care facility received Seroquel 400 mg twice daily instead of 200 mg twice daily. The nurse misunderstood the hospital's summary sheet, compiled from the MAR listing, which listed the dose as 'Seroquel 2 tablets = 200 mg, bid'. The nurse thought this entry meant that the patient should receive two tablets of the 200 mg strength. Another patient received Risperdal (risperidone) 0.25 mg twice daily because the medication entry was listed as '0.5 tablet = 0.5 mg twice

daily'. In this case, the nurse thought the patient was supposed to receive half of a 0.5 mg strength tablet, but in the hospital, the patient was receiving half of a 1 mg tablet. To minimise problems, do not include the tablet strength or liquid concentrations used in the hospital to provide the patient's dose on discharge lists. Instead, include only the drug name, dose, route of administration, and frequency that each medication should be given.

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