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An update in acute liver failure: when to transplant and the role of liver support devices

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Definition

Acute liver failure (ALF) is a syndrome manifest by the rapid cessation of normal function in individuals with previously normal livers. The rate of decline dictates the manner in which the syndrome manifests and influences the outcome. The aetiology is the main influence on the rate of deterioration in function and the likelihood of spontaneous recovery.[1] The rate of decline in function is usually described from the onset of jaundice to the first signs of hepatic encephalopathy; this represents the defining point in the diagnosis of ALF. Classification of ALF has been refined over the years since the original classification at the beginning of the 1970s.[2] The most recent and widely accepted iteration splits ALF into three groups according to the rate of onset (Table 1).[1]

Changing pattern of aetiology in the UK and USA

Within the UK, and as recently reported in the USA, paracetamol hepatotoxicity is the leading cause of ALF, followed by liver failure of unknown aetiology or seronegative hepatitis.[3,4] Viral hepatitis remains the most prevalent form within the developing world.[5] Over the last 30 years the pattern of ALF within the UK and USA has changed.[3,4] In the UK, paracetamol overdose (POD) is almost invariably due to deliberate self-harm. In contrast, the USA data suggest that over half the cases of ALF due to POD are caused by therapeutic misadventure. Some doubts have been expressed regarding this interpretation, suggesting that some patients in the misadventure group may in fact be occult suicide attempts.[4,6]

Until the late 1990s the rate of hospital admission due to paracetamol ingestion had risen year on year. In 1998, legislation was introduced in the UK in which over-the-counter sales of paracetamol were restricted to tablets in blister packs (16 tablets from most retail outlets and 32 from pharmacies). Since then the rates of admission to hospital, severe liver toxicity and transplantation for POD have fallen.[7]

These changes have occurred on a background of a reducing incidence of acute viral hepatitis, especially hepatitis A. In our unit, however, there has been

Table 1. Classification of acute liver failure.

	Time from onset of symptoms to encephalopathy	Common aetiologies
Hyperacute liver failure	<7 days	Paracetamol hepatotoxicity Hepatitis A, B
Acute liver failure	28–7 days	Hepatitis A, B, E Idiosyncratic drug reaction NANB hepatitis
Subacute liver failure	28–5 weeks	NANB hepatitis

NANB = non-A non-B hepatitis.

an increase in the incidence of ALF induced by acute hepatitis E, with three confirmed cases over the last year. It is unclear if this trend will continue, but hepatitis E is increasingly recognised as a significant cause of both sporadic and epidemic hepatitis worldwide.[8]

Indeterminate non-A non-E hepatitis (NANB) seronegative ALF is often presumed to be viral in origin and is the most common presentation (excluding POD) in the UK and USA. NANB can be conveniently thought of as a single entity because of the similar way it presents and progresses. In reality, it is probably an amalgam of various causes, including acute presentations of autoimmune hepatitis, idiosyncratic drug reactions and viruses.[9,10] It is a diagnosis of exclusion and is continuously being 'chipped-away' with better characterisation of aetiologies, resulting in a falling incidence in some centres.[3] There has been a small decrease in our centre since the late 1990s.

Medical management

The medical management of ALF can be differentiated into general supportive care and specific therapy aimed at the causes and complications of liver failure:

- *Supportive care* should be provided by a multidisciplinary team with experience in the management of ALF and access to a transplant programme.
- *Specific therapy* is focused towards those aspects of monitoring and organ support associated in particular with ALF. Emphasis is placed on immune failure and prevention of infectious complications, early renal support, and the recognition and management of intracranial hypertension.

Despite the relative rarity of the syndrome there have been several reported improvements in the intensive care management of patients with ALF over the last few years, particularly focused on the management of intracranial hypertension.[11-13] (For recent reviews see Refs 14 and 15.)

Transplantation

When and who to transplant

Following the first transplants for ALF in the early 1980s the numbers transplanted for paracetamol toxicity rose steadily, reaching a plateau during the early 1990s. After the introduction of the paracetamol legislation in 1998 the numbers initially reduced but data from UK Transplant suggest this may have been a temporary fall (Fig 1).[16]

Transplantation has had a huge impact on the management of ALF. It remains

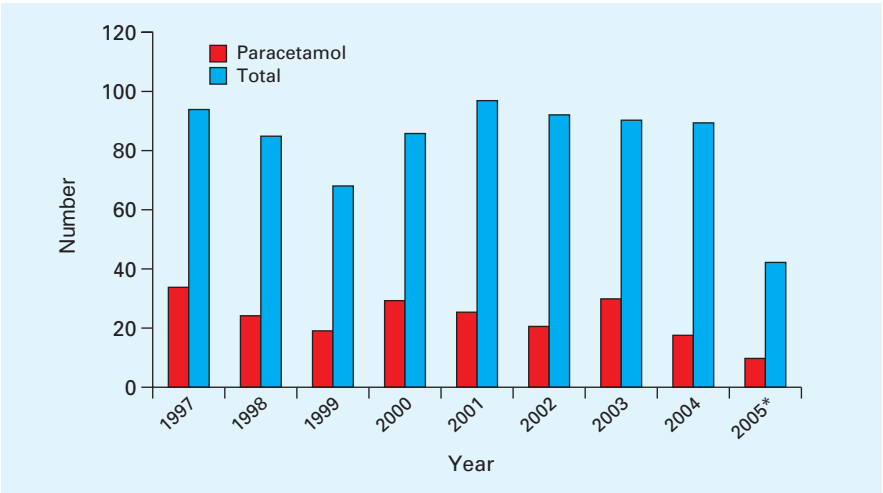

Fig 1. UK Transplant data on super-urgent transplants attributable to acute liver failure (1997 to July 2005).[16] *Incomplete data.

Key Points

Acute liver failure is a syndrome induced by differing aetiologies that dictate the rate of onset, clinical presentation and eventual outcome

The most common cause worldwide is viral hepatitis. The most common cause in the UK is paracetamol hepatotoxicity

Acute liver failure due to paracetamol has decreased over the last 10 years in the UK following the introduction of legislation on pack type and size

There is a super-urgent category in the national transplant indications available for patients with acute liver failure who, because of their condition, are not able to wait

Prognostic markers are used to assess the likelihood of survival as early as possible following presentation to provide the best chance of successful transplantation

The severity of organ failure in the recipient and the quality of the donor liver are predictors of outcome following transplantation

Auxiliary transplantation in which part of the native liver is left in situ is possible in some patients with the hope of regeneration and eventual withdrawal of immunosuppression

Artificial liver support can be split into biological and non-biological. Biological systems contain cells and attempt to provide some or all the functions of the native liver, while non-biological support essentially represents detoxification

Both forms of support are experimental

KEY WORDS: acute liver failure, auxiliary, biological, fulminant hepatic failure, hepatic support, non-biological, paracetamol, super-urgent, transplant criteria, viral hepatitis

the only treatment option for patients with significant liver failure. Some patients, however, deteriorate very rapidly and will die whatever management strategy is used, while the majority will recover and regain normal or near normal liver function. Timing is important; in those with severe injury, there is a window of opportunity beyond which transplantation often becomes futile.[17]

Super-urgent criteria

A 'super-urgent' designation was defined so that patients with ALF would not be precluded from transplantation. This designation is applied nationally and patients placed on the transplant list as super-urgent will receive the next available appropriate liver. The prognostic criteria on which the super-urgent designations are based have been reached by a process of consultation and consensus among the UK centres (Table 2). They were developed using retrospective multivariate statistical analysis of large databases of patients with ALF. These criteria were then applied in a prospective manner to enable validation.[18] While not perfect, they have subsequently been validated in other centres and shown to be robust.[19] Other criteria have been developed and are used in other countries based on their particular cohort of patients.[20]

There are two problems with the original criteria. First, despite their good specificity (ie if the patient achieves these criteria they are likely to die), the sensitivity and negative predictive value are less good and a substantial proportion of patients will die without ever reaching transplant criteria. For example, a pH below 7.3 has a sensitivity of only 0.50 following POD. Awaiting positive criteria can lead to delay in listing and worsening of organ failure that often then precludes listing. This contributes to published rates of transplantation in those who reach the criteria being only 50% following POD.[21]

Secondly, clinical practice has changed since the criteria were defined. For example, it is rare to see a patient with a pH below 7.3 after POD or a creatinine above 300 mmol/l because of improved resuscitation and early renal support at the referring hospital. As a result, research effort has continued to establish markers that increase sensitivity and occur even earlier in the course of the syndrome, while maintaining good specificity and not reducing the positive predictive value to unacceptable levels leading to unnecessary transplants.

Prognostic markers

Serum phosphate levels are higher in non-survivors following POD and in other causes of ALF.[22,23] In fact, survivors or patients with significant liver regeneration exhibit low serum phosphate levels. There appears to be an unacceptable overlap and it has been suggested that serum phosphate does not provide any additional benefit to existing markers.[24–26]

Metabolic acidosis is a good prognostic marker in POD. The mechanism is multifactorial but a major component is serum lactate. The liver plays a central role in lactate metabolism. In patients with severe liver necrosis the liver changes from being a net consumer of lactate to a net producer.[27] Arterial blood lactate levels improve the sensitivity and maintain the specificity if added to the original King's College Hospital (KCH) criteria; they can be achieved earlier in the course of the syndrome and have been widely accepted.[28]

Table 2. The criteria for super-urgent listing for liver transplantation.

Category	Criteria
1	Paracetamol: pH <7.25 <24 hours after overdose and after fluid resuscitation
2	Paracetamol: coexisting PT >100 sec or INR >6.5, serum creatinine >300 μmol/l or anuria, grade 3–4 encephalopathy
3	Paracetamol: serum lactate >3.5 mmol/l on admission or >3.0 mmol/l >24 hours after overdose and after fluid resuscitation
4	Paracetamol: 2 of 3 criteria from category 2 with clinical evidence of deterioration (eg increased ICP, FiO_2 >50%, increasing inotrope requirements) in the absence of clinical sepsis
5	Aetiology: hepatitis A or B, idiosyncratic drug reaction, seronegative hepatitis. PT >100 sec or INR >6.5 and any grade of encephalopathy
6	Any grade of encephalopathy and any 3 from the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time >7 days, serum bilirubin >300 μmol/l, PT >50 sec or INR >3.5
7	Aetiology: acute presentation of Wilson's disease or Budd-Chiari syndrome. Combination of coagulopathy and any degree of encephalopathy
8	Hepatic artery thrombosis within 14 days of liver transplantation
9	Early graft dysfunction with at least 2 of the following: AST >10,000, INR >3.0, serum lactate >3 mmol/l, absence of bile production
10	Acute liver failure in children: multisystem disorder in which severe acute impairment of liver function with or without encephalopathy occurs in association with hepatocellular necrosis in a child with no recognised underlying chronic liver disease. Children with leukaemia/lymphoma, haemophagocytosis and DIC are excluded. Criteria: INR >4 or grade 3–4 encephalopathy. If paracetamol overdose, adult criteria apply. See categories 1–4.

AST = aspartate aminotransferase, DIC = disseminated intravascular coagulopathy; FiO_2 = fractional concentration of oxygen in inspired gas, ICP = intracranial pressure, INR = international normalised ratio, PT = prothrombin time.

Other factors recently investigated include alpha-fetoprotein (AFP). Following POD, AFP levels increase in survivors earlier than in non-survivors. If peak alanine aminotransferase is used as a reference point, AFP on the following day can be used as a discriminator.[22] These patients often have worse acute physiological variables including haemodynamics, oxygenation and Glasgow coma score, as collated in the critical care prognostic scoring system APACHE II and III.[29]

Prognostic markers are not perfect as they do not use all the available data but are based on expert opinion before investigation. Their inclusion is therefore open to subjective bias.

A number of interesting studies have attempted to address these issues. In one, blood samples taken within six hours of admission in patients with fulminant hepatic failure (FHF) not induced by POD were analysed by nuclear magnetic resonance spectroscopy. Using this technique a model was established with acceptable sensitivity and specificity.[30] This analysis, known as metabonomics, uses all molecules within a sample by means of pattern recognition or neural network analysis. It may improve diagnostic accuracy earlier in the course of the syndrome. It is being applied in other disease states.[31,32]

On the practical issue of managing patients with FHF some room for clinical interpretation has been included in the super-urgent listing rules. For example, there is a group of patients who do not achieve KCH criteria but subsequently die, usually of cerebral oedema or multiple organ failure secondary to sepsis.[33,34] These patients often have worse acute physiology scores than survivors.[21,29] The UK super-urgent criteria allow an assessment of deteriorating acute physiology based on cardiovascular, respiratory or cerebral pathology.

Outcome from transplantation

Data from the European Transplant Registry[35] show that one-year survival in patients transplanted for ALF is worse than for chronic liver disease. The excess mortality is seen within about the first month following transplantation (Fig 2). The curve then flattens and the survival rate becomes better than for patients with chronic liver disease. This probably represents a younger age group and less disease recurrence, although the total proportion surviving at 10 years is smaller. Patients transplanted for seronegative ALF have a better survival profile than other ALF transplanted patients, although they exhibit a similar early mortality while in the intensive care unit.[10] Patients transplanted for POD and other causes of ALF often have worse acute physiological derangements at the time of transplant than those with NANB hepatitis.

Prediction of early mortality

A few attempts have been made to determine whether early mortality following transplantation in ALF can be predicted. Severity of acute physiology and amount of organ support in the recipient is a likely predictor of outcome following transplantation, but precise criteria on which to base this have been difficult to define, mainly because the data are confounded by either not listing unstable patients or removing them from the list. Age is also a significant factor – certainly for seronegative ALF, but in POD age is often used to exclude listing.[21] It seems that both recipient and donor factors may help to predict the outcome from transplantation due to both POD and seronegative ALF.[10,21,32,36] A number of both kinds of factors were important in a retrospective analysis of the first 100 patients transplanted for ALF at KCH.

Recipient factors. Two-month survival was predicted in non-paracetamol induced ALF by serum creatinine at the time of transplantation and in paracetamol-induced ALF by the time from ingestion to transplant. All patients transplanted later than six days from ingestion died.

Donor factors. APACHE III score at transplantation and the severity of metabolic acidosis are also predictive.[36] Other important donor factors are the use of reduced size grafts in paracetamol-induced ALF and evidence of early graft dysfunction, as defined by a high aspartate aminotransferase or international normalised ratio, in the early postoperative period. In addition, a high donor body mass index is a risk factor for death in seronegative ALF, pointing towards fatty liver or initial graft dysfunction.[10,21]

The data are mixed and contradictory but, although it is difficult to be certain, they suggest that older recipients with severe pre-operative organ dysfunction are less able to tolerate any initial graft dysfunction. This points to matching of the organ to the recipient, as has been suggested in both chronic liver disease and seronegative ALF[32,37] – in reality, a luxury not an option in ALF due to time constraints.

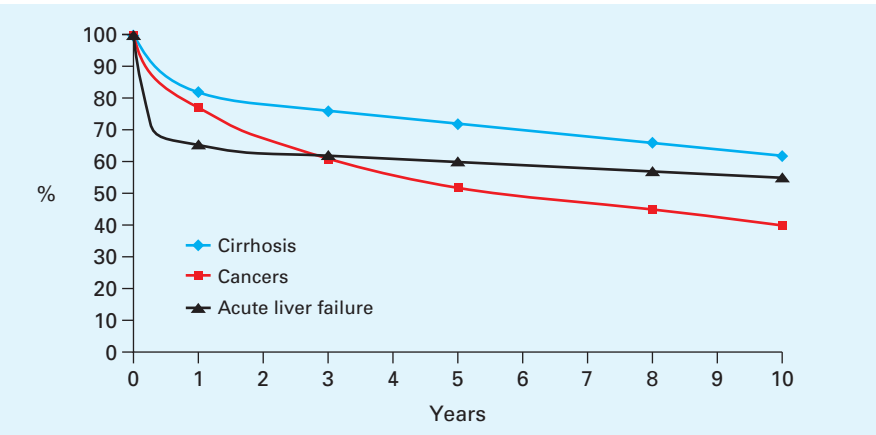

Fig 2. Patient survival according to the first indication of liver transplantation (January 1988 to December 2003).[35]

Auxiliary transplantation

Auxiliary partial liver transplantation has many theoretical advantages over standard orthotopic transplantation in ALF. It provides the potential both to support the patient during the acute phase of liver failure and to enable regeneration of the native liver. This is attractive, offering the potential to withdraw immunosuppressive therapy, allow the graft to atrophy or be removed and eliminate the risks associated with lifelong immunosuppression.

Data on this procedure have been accumulating over the last 10 years. Initial reports suggested that the procedure was associated with a high incidence of technical problems, primary dysfunction and retransplantation. Later reports indicate that many of these issues are resolving with greater experience, patient and graft selection. The best outcomes have been in patients aged below 40 years with either acute viral hepatitis or paracetamol hepatotoxicity. One-year graft and patient survival is similar to standard transplantation for ALF. Withdrawal of immunosuppression can be achieved in 30–70% of patients.[38–40]

When not to transplant

The decision to offer liver transplantation cannot be made solely on the basis of abstract predictors of survival. Life following transplantation is not normal. The burden of lifelong immunosuppression both on physical and psychological health cannot be underestimated. Many patients who present with ALF due to POD are chaotic, with multiple social and psychiatric problems, often mixed with concurrent alcohol abuse and higher levels of social deprivation.[41] These factors make listing decisions difficult, especially with the time available, and it is clear that there is considerable filtering of patients at an early stage in all transplant centres. The basis for this is not well defined and the patients not transplanted inevitably bias any outcome data. In Bernal's study[21] on the use of transplantation in ALF, four patients (12% of those transplanted) died of deliberate self-harm during follow-up. No pre-operative factors were predictive of postoperative suicide. There is a need for greater debate in this area.

Liver support systems

The fulminant nature of the syndrome, the scarcity of organs and potential for delay in transplantation, together with the promise of full recovery in many patients, particularly in the case of paracetamol hepatotoxicity, all suggest a role for some form of liver support system as a bridge to either recovery or transplantation. Supporting the liver is not simple; it is a complex organ. To be an ideal liver replacement, any system has to support a wide range of biosynthetic, metabolic and eliminatory functions (Table 3). Additionally, any successful system will have to counter the systemic effects of the dying and necrotic liver as well as the effects of functionally altered hepatocytes – the toxic liver hypothesis.[42]

There has been a relatively long history of extracorporeal support for failing liver. Early attempts were cross-circulation with animals and investigation of various dialysis techniques. Current research activity follows two broad approaches:

- the use of biological systems with live hepatocytes, and
- non-biological blood purification using adsorption and dialysis techniques.

Biological

Biological systems are the logical approach to developing an ideal liver replacement system. The aim is to replace all or most of the functions of the native liver and to incorporate cells with hepatocyte-specific functions. Data from liver resection suggest that approximately 250 ml of liver by volume is required to prevent death from liver failure, typically representing 20–30% of liver mass.[43]

There have been several approaches to the supply of cells for an extracorporeal system:

- *Primary hepatocytes*, both animal and human. They outperform other cell lines in terms of metabolic function but tend to lose hepatocyte specificity in culture. Concern about zoonosis limits research into animal cells.
- *Hepatocytes derived from immortal cell lines* offer the advantage of being readily available for use from cell culture but, in general, have poor function compared with primary cells. Immortalised hepatocyte cell lines that proliferate in culture while retaining their liver specific functionality have been created by retroviral transfection with regulatory genes that stimulate cell division. Obvious apprehension regarding the introduction of potentially 'cancerous' cell lines has stimulated research into the use of 'terminator' genes that give the cells a limited life or enable the immortalising gene to be switched off.[44] Other sources of immortal and readily cultured cells are tumour derived, such as the ubiquitous Hep G2/C3A hepatoblastoma line. Stem cell sources appear to offer the most hope but are still some time from becoming available.[45]

Clinical trials. Clinical trials with bioartificial liver support systems have generally

Table 3. Functions of the liver.

- Excretion of bilirubin, cholesterol, hormones and drugs
- Metabolism of fats, proteins and carbohydrates
- Enzyme activation
- Storage of glycogen, vitamins and minerals, and regulation of glucose levels
- Synthesis of plasma proteins (eg albumin, clotting factors) and bile production
- Blood detoxification and purification
- Immune regulation

been disappointing. The two systems most widely studied are the Extracorporeal Liver Assist Device (ELAD) and Bio-artificial Liver (BAL) systems. The largest trial published to date using a bioartificial liver, which reported recently,[46] was terminated early by the Data and Safety Monitoring Board because results at interim analysis suggested it was likely to be futile.

A further study has been requested by the US Food and Drug Administration before approving the device. The ELAD system uses a hepatoma cell line and has been investigated in a number of phase I studies. The first, a randomised study, reported in 1996, showed no difference in outcome.[47] A further phase I randomised controlled trial (RCT), using an updated version of the ELAD with a much greater mass of hepatocytes, has reported in abstract form. It was not powered for mortality, but showed show a trend for improved survival in the treatment group.[48]

Non-biological

At a simple level, accumulation of toxins during ALF can be considered to be the pathophysiological basis for the syndrome. Many chemicals that accumulate within the blood during ALF are small or middle-sized molecules[42] which can be targeted by a variety of techniques. These include dialysis through various types of membrane, adsorption on to carriers such as charcoal, resins or albumin, and a combination of these. Non-biological systems are attractive because they are relatively inexpensive (compared with biological) and logistically much easier to implement.

Direct adsorption via charcoal haemoperfusion was investigated at KCH during the 1970s and early 1980s. Initial trials were encouraging but larger RCTs failed to show improvement in outcome.[49]

Adsorbents have been added to the dialysis fluid to improve the efficacy of dialysis-related procedures – to widen the range of molecules removed (ie both water soluble and insoluble molecules). The two most extensively studied are charcoal suspension in the BioLogic-DT™ system and 20% albumin in the MARS™ system. Both the BioLogic-DT and MARS have been shown to improve haemodynamic parameters and short-term encephalopathy scores in patients with acute-on-chronic liver failure (AOCLF). The results of studies into their utility in ALF are less clear, with inconsistent results from small uncontrolled series and case reports. MARS therapy is associated with increased peripheral vascular resistance and concomitant reduction in cardiac index. However, the effect may be short-lived and there appears to be no consistent effect on intracranial hypertension.[50,51] Similar results have been reproduced with high volume haemofiltration, emphasising the need for comparative RCTs.[52] A recent meta-analysis of all RCTs in non-biological liver support concluded that short-term mortality in AOCLF is improved but that this could not be shown in ALF.[53]

Conclusions

Liver transplantation remains the only definitive form of treatment for severe ALF but is applied in a relatively small number of patients presenting with the syndrome. Overall survival is worse than that in chronic liver disease because of the severity of illness at presentation, but predicted survival of less than 15% in those who reach transplant criteria is improved to approximately 65% overall at one year. Improvements in surgical techniques and the use of auxiliary grafts may lead to an improved outcome in this group, with the possibility of stopping immunosuppression following native regeneration in selected patients.

Liver support systems remain at the experimental stage. Biological systems that provide all or most of the native liver function are still being actively investigated and offer a potential support system that may bridge patients to native recovery. The availability of effective, stable cell lines remains elusive. The concept of non-biological extracorporeal 'toxin removal' remains unproven in ALF. Many systems over the years have shown early promise but have been unable to sustain this over time. The idea remains attractive and is actively investigated by each new generation of hepatologists. Adequately powered RCTs are needed to settle the argument whether this form of therapy will ever be effective in bridging to either transplantation or recovery.

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