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Short Reviews on Liver Transplantation

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Liver transplantation in adults with acute liver failure

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1. Selection of transplantation candidates

The only therapeutic intervention of proven benefit for patients with advanced acute liver failure (ALF) is that of emergency liver transplantation (LT) [1]. However, there can be few more difficult decisions in hepatology than that to list and transplant a patient with ALF. Often it must be taken with limited clinical and background information and in the presence of rapid clinical deterioration, where delay could result in a patient becoming un-transplantable due to the development of clinical contra-indications. The risks of emergency transplantation in the context of evolving or established multiple organ failure (MOF) must be balanced against the possibility of survival with continued medical supportive care alone. The consequences of inaccurate selection for transplantation are huge; a false positive selection test will result in unnecessary transplantation in a patient who would otherwise survive with medical management, surgery with a 30–40% 1-year mortality and a lifetime of potentially dangerous immunosupression. A graft that could be used in elective transplantation will be lost and major, unnecessary expense incurred. The consequences of a false negative selection test are even greater, resulting in a missed transplant candidate and a likely preventable death.

A variety of selection criteria are in use world-wide, and their comparative accuracy and ease of use are debated [2–5]. As with all diagnostic tests, the best evidence to support the use of particular criteria is from the confirmation of its performance in validation studies [6]. However, the accurate assessment of these selection criteria in such studies is limited by the low methadologic quality of many of the series reported [7]. Bias is introduced both by aspects of study design, and by the very nature of the condition under investigation. ALF is rare even in most transplantation centres, and consequently most reports are of small numbers of patients, usually unblinded and retrospective and over periods of a decade or more, during which time medical supportive management may have changed substantially. Further bias is frequently introduced by the inclusion of transplanted cases as 'non-survivors', an assumption which may be incorrect. All these sources of bias will tend to overestimate the accuracy of the selection criteria under study [8]. With these limitations in mind, the most commonly applied selection criteria will be discussed below.

2. The Clichy criteria

The Clichy criteria (Table 1a) were derived from the multivariate analysis of prognostically important variables in a cohort of 115 patients with fulminant hepatitis B infection, managed medically in the pre-transplantation era between 1972 and 1981 [9]. This analysis revealed age and factor V level to be the most important predictors of survival. Transplantation is recommended if in the presence of coma or confusion (equating to encephalopathy grades 3–4) with a factor V level $<20\%$ in patients under 30 years of age or $<30\%$ if over 30 years of age [10]. In comparison to the Kings College Hospital (KCH) criteria, validation studies are scarce, but nonetheless the Clichy criteria are in use in much of Northern Europe. Their more widespread use has been limited by two main factors. Firstly, the expense and limited availability of factor V level measurement outside certain centres, and secondly that their derivation was from a cohort of patients with ALF resulting from a single aetiology. As will be discussed below, aetiology may play a major role in determining the outcome of the illness. Subsequent comparative studies have suggested performance in acetaminophen (paracetamol)-related disease to be inferior to that of the KCH criteria [11], and indeed limited in many patients with non-paracetamol-related disease [12,13].

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3. The Kings College criteria

In deriving the KCH criteria [14], O'Grady examined prognostically important variables in a retrospective cohort of 588 patients managed medically during 1973–1985. The findings were subsequently validated in 175 patients with ALF treated between 1986 and 1987. Importantly, he recognised the role of both aetiology and mode of presentation in determining the possibility of recovery with medical supportive therapy alone. By example, in patients with acetaminophen-related ALF in whom the interval between the development of jaundice and onset of encephalopathy is short (a 'hyper-acute' presentation) survival with medical management may be surprisingly good. By contrast, other aetiologies such as 'sero-negative' hepatitis or drug-induced ALF and a more indolent or 'sub-acute' presentation are associated with a dismal survival without transplantation [15]. The KCH criteria therefore differentiate between patients with acetaminophen-induced hepatotoxicity and other causes of ALF (Table 1b), and have been widely adopted [16].

More published data exist to support the use of the acetaminophen than the non-acetaminophen criteria. Studies relating to acetaminophen have recently been assessed and subjected to meta-analysis [17], which confirmed many of the previously established impressions of their clinical performance (Table 2). Firstly, that the criteria have a clinically acceptable specificity, the patient who fulfils the criteria is very likely to die without transplantation. Survival with medical management alone in this group is between 10 and 15% in most series [18–21]. Secondly, that their sensitivity is relatively limited in that a proportion of patients will die without fulfilling criteria and thus without prior identification and consideration as potential transplantation candidates [18,19]. A third issue, not identified in the meta-analysis but shown to be of major importance in a number of clinical series is that the rate of clinical deterioration is so great that in almost 50% of patients fulfilling criteria, transplantation is never a realistic option either due to the presence of contra-indications to transplantation at the time of fulfilling criteria or to their development whilst awaiting a graft [18,22].

In comparison to the acetaminophen data, there are fewer published studies evaluating the performance of the non-acetaminophen criteria and have been recently summarised [2]. Their performance again shows acceptable specificity, but the most consistent finding of these studies is of a low negative predictive value (<0.6 in most studies), i.e. that if a patient does not fulfil the criteria, the probability that he or she will survive with medical management alone is limited. This is reflected by a greater proportion of deaths in patients who do not fulfil the criteria.

Table 1a
The Clichy criteria

Transplantation if:
- Coma and confusion (encephalopathy grade 3 or 4) and
- Factor V < 20% if under 30 years or
- Factor V < 30% if over 30 years

Source: Ref. [10].

Table 1b
The Kings College criteria

Non-acetaminophen (paracetamol) aetiology
Transplantation if:
- INR > 6.7 or
Any three of
- Unfavourable aetiology (drug, seronegative)
- Age <10 or >40 years
- Acute/subacute presentation
- Bilirubin >300 μmol/l
- INR > 3.5
Acetaminophen aetiology
Transplantation if:
- Arterial pH <7.3 after volume resuscitation or
Concurrent findings of
- Encephalopathy of grade III or above
- Creatinine >300 μmol/l
- INR > 6.5

Source: Ref. [14].

Table 2
Meta-analysis of performance of Kings College criteria for acetaminophen

Criteria	No. of studies	Pooled sensitivity, % (95% CI)	Pooled specificity, % (95% CI)
Kings	8	69 (63–75)	92 (81–97)
pH <7.3	4	57 (44–68)	89 (62–97)
Combined	3	55 (44–66)	94 (90–98)

Source: Ref. [17].

4. Alternative prognostic markers

To address the clinical problems with the use of established criteria and improve selection of transplant candidates, alternative or additional prognostic markers are required. An ideal prognostic marker in this setting would be simple to determine, could be rapidly, safely, accurately and reproducibly measured and its addition to other established criteria would identify patients earlier and result in an increase in sensitivity and negative predictive value without lowering specificity. To this end, a wide variety of blood markers have been proposed including factor VIII and V ratios [23], serum levels of Gc protein [24], serial prothrombin times [25], and arterial ketone body ratio [26], although until recently, none had shown all these ideal characteristics. Practical difficulties may limit the utility of other investigations of potential prognostic value; though

a liver volume of <1000 ml on CT scanning is associated with very poor survival [27], such imaging is frequently contra-indicated by the patients clinical condition. Similarly, though the extent of observed hepatic necrosis on liver biopsy may bear some relation to outcomes [27,28], the biopsy procedure may be hazardous and histopathological heterogeneity may lead to misleading results on percutaneous or transjugular samples [29].

Two developments have recently been described in patients with acetaminophen-induced hepatotoxicity. Blood lactate has recently been shown to have a close relation to survival in ALF [30]. Elevations in blood lactate in this setting are likely to reflect the combination of increased systemic production in multiple organ dysfunction and impaired hepatic clearance following hepatic injury. The addition of blood lactate measurements to the KCH criteria improved sensitivity and time of identification without appreciable reduction in sensitivity. Similarly, hyper-phosphateamia has recently been reported to be an accurate early predictor of poor outcome in severe acetaminophen-induced hepatotoxicity [31]. In this setting, it may reflect the combination of renal impairment and a lack of substrate utilisation due to a failure of hepatic regeneration. Again, the addition of phosphate measurements to the KCH criteria appeared to improve sensitivity and time of identification without appreciable reduction in specificity, although the 98% overall test accuracy initially reported has not been reproduced elsewhere [32]. The introduction of both lactate and phosphate measurements into selection criteria should, however, await confirmation of their performance in further appropriately conducted validation studies.

5. Liver transplantation

The overall results of LT in patients with ALF have improved significantly since the introduction of the technique. However, the outcome remains worse than those transplanted for chronic liver disease (Fig. 1). This is primarily as a result of the high early post-operative mortality in patients transplanted for ALF. Most deaths in this period are now as a result of sepsis and MOF [33,34], with early neurologic deaths [10] becoming less common, perhaps as a consequence of increased intra- and peri-operative monitoring of intracranial pressure and improvements in the management of cerebral oedema.

Two interacting factors are likely to influence the outcome of transplantation in this setting. These are the severity of pre-transplant illness of the recipient, and the nature of the graft used. The critically ill recipient has a particular vulnerability to the consequences, particularly infectious, of poor early graft function.

The more unwell a patient is, either in terms of the severity of encephalopathy or overall MOF, the less likely

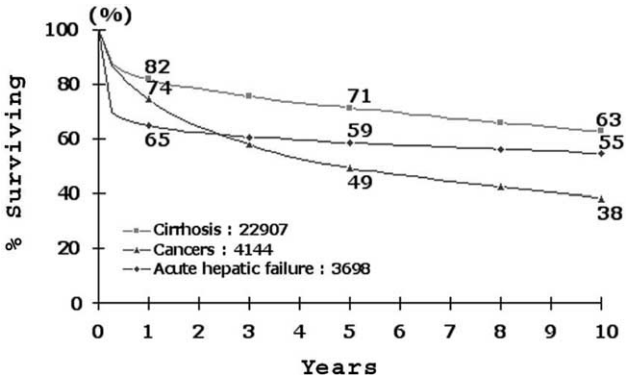

Fig. 1. Patient survival according to the first indication for liver transplantation in Europe, January 1988 to December 2001. Source: European Liver Transplant Registry, October 2003 (http://www.eltr.org/publi/results).

that transplantation will be performed and that the surgery will be successful [10,18,35]. A review of 100 transplants performed for ALF at KCH showed that the severity of MOF at the time of transplantation was single best predictor of patient survival [35].

This severity varies by the aetiology of ALF, and is greatest in those with acetaminophen-related disease [35]. In a series of over 300 patients listed for LT in Scandinavia, deaths whilst awaiting LT were more than twice as common in those with acetaminophen-related disease than in those patients listed for ALF due to other aetiologies [36]. In a series from KCH [18], 45% of patients fulfilling KCH criteria with acetaminophen-related disease had such severe MOF that listing for transplantation was not an option; more than 90% of these patients died. Furthermore, 35% of the patients who were listed for transplantation did not undergo surgery and in the majority of cases this was because of the development of clinical contra-indications whilst awaiting a graft.

The second major factor shown in most series to be important in determining outcome is that of the nature and quality of the graft used. This is illustrated by the early Hospital Paul Brousse experience where the first available graft was used for patients with ALF, regardless of size, quality or blood group compatibility [10]. Analysis of 116 transplants showed strong effects of graft factors upon patient and graft survival, with markedly inferior outcomes in those patients receiving marginal, size reduced or ABO incompatible grafts.

A successful outcome is most likely to occur where recipient and graft are individually matched; a sick patient will do best if they receive an optimal graft. A difficult balance must be struck between the risk of delaying transplantation until an appropriate graft is available, with the likelihood of further clinical deterioration before that time, and the earlier acceptance of sub-optimal grafts that may be associated with a poorer outcome.

6. Auxiliary liver transplantation

Auxiliary liver transplantation (ALT) has many theoretical attractions for ALF. In this technique, a partial liver graft is placed either heterotopically or orthotopically while leaving all or part of the native liver in situ. With resolution of the insult causing ALF, the native liver may subsequently regenerate allowing withdrawal of immunosuppression and graft atrophy or removal, improving quality of life and avoiding long term side-effects and costs. This may be possible in more than half of all ALT recipients [37–39]. A technically demanding procedure, initial reports of ALT showed relatively high rates of anastamotic complications and retransplantation [37], although recent outcomes have improved substantially. In part this is likely to relate to improvements in surgical technique, but also from patient selection. Most centres would now consider ALT only in patients <40 years of age, with limited and stable extra-hepatic organ dysfunction and with the availability of an optimal graft. The prediction of those patients in whom regeneration of the native liver is likely to occur is difficult, and interestingly appears to bear little relation to the histological extent of hepatic necrosis or the presence of fibrosis or regenerative nodules [38]. The best predictors appear to be patient age and the aetiology and mode of presentation of ALF. Regeneration seems to occur best in young patients who have a hyper-acute presentation and a viral or acetaminophen aetiology, the group in whom spontaneous survival is also most likely [15,36,38]. The maturity of this technique and its medical supportive care is well illustrated by recent reports of successful outcomes of ALT using non-heartbeating donors [40], and ALF resulting from acute hepatitis B infection [39].

7. Living donor transplantation

Living donor liver transplantation (LDLT) is now an established part of elective transplantation of paediatric recipients, and as a consequence of the scarcity of cadaveric organs is increasingly being used in adults [41]. Its use in the paediatric ALF population is now well established, though patient and graft outcomes remain inferior to conventional cadaveric transplantation [42,43]. Its extension to the adult ALF population is now being explored, and a number of cases and case series have been reported [42,44–46]. In common with elective transplantation, the primary obstacle to be overcome when adopting LDLT for adult populations with ALF is that of obtaining an adequate size liver graft. In ALF poorer patient and graft survival is seen in patients receiving 'small for size' grafts with a graft to recipient weight ratio (GRWR) $<0.8\%$; an optimal value of GRWR would appear to be closer to 1.0% [42]. Since this is usually impossible to achieve with a left lobe or left lateral segment graft, most successful reported cases of LDLT in ALF have utilised right lobe grafts. The potential advantages of LDLT in this setting are the increase in the speed of availability of a high quality organ for transplantation, and it appears logistically possible to accomplish donor medical and psychiatric assessment in <24 h [42,46]. However, the ethical aspects of this situation are even more complex than those seen in paediatric transplantation where the donor is most frequently a parent and utilises a left lobe graft [47]. Complications are substantially more common in those donating a right rather than left lobe [48] and the pressures upon a candidate donor who is a family member or 'significant other' may be quite different. The pre-donation ethical and psychological evaluation becomes even more important in this setting. Though its application in areas where cadaveric transplantation is rarely undertaken is likely to be common, it is unclear whether the technique will find a place where rapid procurement of cadaveric grafts is already possible.

8. Future directions

A variety of extra-corporeal supportive devices have been advocated to replace liver function in the patient with ALF either to stabilise the patient awaiting transplantation, or to improve native liver regeneration. Despite frequent uncontrolled case series, conclusive evidence of benefit to patients has never been demonstrated [49]. Currently there is no published data to support the use of either biological or non-biological systems in ALF outside the setting of randomised controlled trials.

The use of hepatocyte transplantation (HT) has also been proposed for similar purposes in ALF [50]. In this technique, human hepatocytes are infused into the splenic or hepatic portal vascular beds to provide adjunctive hepatic function for the failing liver. Though there have been reports of the successful treatment of inborn errors of hepatic metabolism using this technique [51,52], the challenges for its extension to ALF are great. The hepatocyte mass required to support or replace lost liver function in ALF is likely to be at least an order of magnitude greater than that required for the correction of isolated metabolic defects [53] and sustaining the viability and function of infused cells in the unfavourable environment presented by sick patients with ALF is likely to be difficult. Case series to date have shown the practicality of the technique although evidence for clinical benefit is limited [54–56]. The successful clinical application of HT in ALF will require optimisation of the process in the non-acute setting and will probably be appropriate only in the most stable patients.

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