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# **The Changing Face of Liver Transplantation for Acute Liver Failure: Assessment of Current Status and Implications for Future Practice.**

MC Donnelly, PC Hayes, KJ Simpson

Dept. of Hepatology, Division of Clinical and Surgical Sciences, University of Edinburgh and Scottish Liver Transplantation Unit, Royal Infirmary of Edinburgh, EDINBURGH. EH16 4SA United Kingdom.

## *Abstract*

The etiology and outcomes of acute liver failure have changed since the definition of this disease entity in the 1970s. In particular, the role of emergency liver transplantation has evolved over time, with the development of prognostic scoring systems to facilitate listing of appropriate patients, and a better understanding of transplant benefit in patients with acute liver failure. This review examines the changing etiology of acute liver failure, transplant benefit, outcomes following transplantation and future alternatives to emergency liver transplantation in this devastating condition.

## *Introduction*

Acute liver failure (ALF) is a rare condition resulting from the sudden loss of hepatic parenchyma and metabolic function. In the United States, ALF is estimated to affect 2000 people per year<sup>1, 2</sup>, with the incidence in the United Kingdom reported at 1-8 per million population<sup>3</sup>. Incidence in the developing world may be higher, but data are lacking. ALF was originally considered a fatal disease. However, around 60-75% of patients should now be expected to survive due to increased utilization of emergency orthotopic liver transplantation (OLT) and improved medical and intensive care management<sup>4, 5</sup>. ALF is an uncommon indication for OLT, accounting for 8% of all liver transplants carried out in Europe between 1988-2009<sup>6</sup>, and 3.9% of listings for OLT in the US between 1995-2005<sup>7</sup>. Utilization of OLT is limited by accurate and timely identification of appropriate patients, the development of contraindications on the waiting list and the unavailability of a graft. In this review article we discuss the current challenges in the field of liver transplantation for ALF, suggesting future directions for research and clinical work.

## *Defining ALF*

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Trey and Davidson<sup>8</sup> originally defined the condition in the early 1970s as the development of hepatic encephalopathy (HE) and coagulopathy in the setting of an acute liver injury, in the absence of chronic liver disease (CLD). Subsequently, several revised definitions have been suggested. A recent systematic review<sup>9</sup> highlighted the heterogeneity of current definitions of ALF in the literature: 41 separate definitions of ALF had been used in 87 different studies. The main components accounting for the differences included the presence and/or grade of HE, interval between onset of symptoms or jaundice and development of HE, the severity of coagulopathy and the occurrence of pre-existing liver disease. No definitive consensus exists, although most studies would consider an INR >1.5 to represent coagulopathy and any grade of encephalopathy to represent ALF. There is a real need for unifying diagnostic criteria for ALF to facilitate a consistent approach to the clinical management of ALF and related research. Consensus on the definition of ALF and ensuring its universal application would be a first step to improving generalisation of clinical research into this rare condition.

HE is usually considered the defining clinical feature of ALF, differentiating cases from those with acute liver injury (ALI). Patients with ALI have sudden, significant liver injury and coagulopathy but no HE. In the US, patients with ALF are listed for urgent transplantation on meeting the United Network for Organ Sharing (UNOS) Status 1a listing criteria for ALF<sup>10</sup>. To assign an adult Status 1a, the presence of HE is a prerequisite. However, pediatric cases can be listed without developing HE<sup>2</sup>. In addition, some patients with certain causes of ALI develop HE late in their clinical course. In such cases, HE is often precipitated by bacterial infection which precludes or delays OLT. Some have argued for listing these patients prior to the development of HE<sup>11</sup>. In the UK, criteria for ALF super-urgent listing have recently been updated<sup>12</sup> allowing listing of patients with unfavorable non-acetaminophen (non-APAP) etiologies (such as those with indeterminate ALF or drug induced liver injury (DILI)) in the absence of HE if the following criteria are met: INR >2 after vitamin K repletion plus any two of; age >40 or <10 years, prothrombin time >50seconds or INR >3.5, or bilirubin >300umol/L (Table 1). These changes are the subject of on-going audit and would also require further assessment and validation in other centres.

#### *Changing etiology of disease*

There are worldwide geographical differences in etiology of ALF. Hepatotrophic viruses (particularly hepatitis B and E) are the most common cause of ALF in developing countries, compared with drugs e.g. acetaminophen (APAP) in the developed world. Such differences in

etiology result from a combination of factors, including endemic presence of hepatitis viruses in the East, cultural differences (e.g. self-medication with APAP is rare in the east) and genetic differences in susceptibility to conditions such as acute fatty liver of pregnancy (AFLP)<sup>13</sup> and APAP overdose<sup>14</sup>.

In 14-20% of patients with ALF, no identifiable cause is found after exclusion of all other potential etiologies by the appropriate investigations<sup>15</sup>. The terminology for ALF without an identifiable cause has evolved over time. Initially, this disease entity was termed non-A, non-B hepatitis, followed by non-A to E hepatitis. More recently, this syndrome has been labeled seronegative hepatitis or indeterminate ALF. For the purposes of this review, indeterminate ALF is the nomenclature of choice. Most cohort studies of ALF report a significant percentage of cases being due to indeterminate ALF, but it remains unclear if this is a distinct but yet unidentified single etiology. Introduction of alternative investigational methodology may reduce uncertainty in this group of patients. The US Acute Liver Failure Study Group (ALFSG) reported that using the APAP adduct test in a group of patients with indeterminate ALF identified occult APAP overdose in 18%<sup>16</sup>. Further work is needed to explore the origins of this disease entity, and formulate and validate a definition that could be universally adopted.

The many causes of ALF have different clinical courses, complications and prognoses and therefore need for OLT. In APAP overdose, ALF has a rapidly progressive course with increased risk of development of kidney injury and cerebral edema, however spontaneous survival rates are higher compared with other causes such as indeterminate cases and DILI. Therefore, difference in incidence of specific etiologies of ALF will influence the utilization of emergency OLT, in addition to the logistical provision of transplantation for such patients in different parts of the world.

Some UK centers have reported a decline in both the total number of APAP related admissions and the severity of disease since the introduction of UK legislation restricting sales of APAP in 1998. A look back study from Kings College, London observed a significant decline in the number of APAP-ALF admissions during 1973-2008 and a reduction in the severity of disease<sup>4</sup>. In contrast, no significant change in the number of APAP admissions was observed in other parts of the UK although an increased frequency of staggered overdoses were reported, an overdose pattern associated with significantly lower spontaneous survival rates in this cohort<sup>17</sup>. A sales restriction on APAP has never been

introduced in the USA, where the percentage of ALF secondary to APAP has increased from 28% in 1998 to 51% in 2003<sup>14</sup>. In a large multicenter US study 48% of APAP-ALF patients were admitted with an unintentional overdose (including unintentional multiple time point ingestion), however in this cohort mortality was not significantly related to overdose pattern<sup>14</sup>.

With regards to other etiologies, the Kings group<sup>4</sup> also reported a significant decline in the number of admissions with ALF secondary to viral hepatitis between 1973 and 2008. Reduced frequency of acute viral hepatitis may have resulted from improved public health measures, more effective and rapidly acting antiviral therapy in acute HBV infection and combined HAV/HBV vaccination. There was no significant change in the number of patients presenting with non-APAP related DILI or pregnancy related disease in the Kings cohort over time. An awareness of the changing etiology of ALF over time is important. The etiology of ALF is undoubtedly related to subsequent need for transplantation. However, in the King College look-back study the use of transplantation significantly increased over time despite the reduced frequency of APAP-ALF, with the proportion of patients transplanted being greater in the non-APAP versus APAP cohort<sup>4</sup>.

#### *Non-transplant management options*

N-acetylcysteine (NAC) has a proven evidence base in APAP poisoning, but there are relatively limited medical, non-transplant therapies available for non-APAP ALF. NAC can improve liver oxygenation and has antioxidant, anti-inflammatory and immunologic effects<sup>18</sup>. NAC also has beneficial hemodynamic effects and may improve cerebral perfusion pressure<sup>19, 20</sup>. Several studies have therefore investigated NAC therapy in non-APAP ALF. Lee et al<sup>21</sup> undertook a prospective, multicenter, double-blind trial comparing intravenous (IV) NAC versus placebo in patients with non-APAP ALF. IV NAC improved transplant-free survival in patients with grade I or II HE but was ineffective in patients with advanced HE. A study undertaken in the pediatric non-APAP ALF population reported that use of NAC did not improve one-year survival<sup>22</sup> and a meta-analysis of the efficacy and safety of NAC in adult non-APAP ALF reported no significant difference in overall survival between the NAC and control groups<sup>23</sup>. However, NAC may still have a role in specific non-APAP ALF etiologies, for example in the management of mushroom poisoning and DILI-ALF<sup>24</sup>. Possible non-transplant management options, including the role of the systemic inflammatory response and infection, are discussed individually in the supplemental material.

### *Assessing prognosis and listing for transplant*

Accurate prognostic models are vital to identify those patients who are most likely to benefit from emergency OLT, at a time when transplant is still feasible. Similarly, the timely prediction of patients likely to survive spontaneously prevents unnecessary OLT and long term immunosuppressant therapy. Lake previously reported that as many as 20% of patients with ALF may be transplanted unnecessarily<sup>25</sup>. A recent systematic review identified survival was 24% in non-transplanted APAP-ALF patients meeting the Kings College Hospital Poor Prognostic Criteria (KCC)<sup>26</sup>. Spontaneous survival rates have improved over time for many etiologies<sup>4</sup>; however prognostic models have not been adapted to account for this. There is a desperate need for better prognostic criteria to maximise the transplant benefit afforded to patients with ALF.

Several prognostic scoring systems have been proposed, validated and reviewed in the literature. Unfortunately all of these models have shown inconsistencies in reproducibility and prognostic accuracy, limiting their clinical utility. This may at least in part be as a result of a heterogeneous patient population and the wide variety of definitions of ALF in such studies. A further problem lies in that many studies investigating prognostic models equate liver transplantation with death; this falsely elevates the positive predictive value of scoring systems. The most widely studied and utilized criteria are the KCC, Clichy criteria and Model for End-Stage Liver Disease (MELD). These are discussed in more detail in the supplementary material.

### *Transplant benefit*

With studies demonstrating increasing spontaneous survival rates in some groups of patients with ALF, the survival benefit afforded by emergency OLT has been called into question. However, there are limited data available to facilitate this type of analysis. Many cohort studies do not report the outcomes of patients reaching poor prognostic criteria who are not transplanted or listed for OLT. Analysis is further complicated by the observations that after reaching poor prognostic criteria many patients are not considered transplant candidates due to medical or psychiatric contraindications, or they may be too sick to be offered emergency OLT. As many as 60% of APAP-ALF patients with poor prognostic criteria may be excluded from OLT due to contraindications compared with 23% in non-APAP ALF cases and consequently the mortality in the former group is increased<sup>27</sup>.

Most would accept that there is a clear survival advantage in patients with non-APAP ALF. Kremers assessed the survival benefit associated with transplant in a US cohort of patients with ALF listed under UNOS Status 1 criteria<sup>28</sup>. In patients with non-APAP ALF, OLT was significantly associated with improved survival, especially in patients with higher MELD scores. In the Scottish cohort overall survival in the non-APAP ALF group was 58.0%, with 71.1% of surviving patients undergoing OLT<sup>27</sup>. In the Kings College cohort<sup>4</sup>, introduction of OLT had transformed the outcome for patients with non-APAP ALF, from 4.2% survival to hospital discharge in 1973-1978 to 67.6% in 2004-2008.

In contrast, the survival advantage conferred by emergency OLT in APAP-ALF is less clear cut, and no formally reported analysis of the survival benefit with OLT in this cohort has been undertaken. In APAP-ALF, outcomes have improved in those patients undergoing transplantation and also in those who are managed medically<sup>29</sup>. O'Grady reports that the median time from listing to acceptance of an organ is 7.5 hours<sup>29</sup>, highlighting the importance of listing only appropriate patients in a timely fashion to prevent unnecessary transplantation. As previously noted, prognostic scoring systems have not been adapted to account for temporal changes in disease epidemiology. The Kings College group suggest that the survival advantage with emergency OLT in APAP-ALF may be as low as 14%<sup>4</sup>. In contrast a survival advantage analysis for the Scottish APAP-ALF cohort with KCC suggests that survival advantage in this cohort with high mortality is considerably higher<sup>27</sup>: survival in the patients who were not considered transplant candidates was 16.7% compared with 78.8% survival in APAP-ALF transplanted patients. However, approximately 50% of cases excluded from emergency OLT were considered too sick to transplant. Clearly other data from different cohorts stratified for disease severity are needed to define survival advantage in both APAP and non-APAP ALF.

#### *Contraindications to listing*

Prognostic scoring systems cannot and should not be used in isolation to identify those patients who could and should be listed for emergency OLT. Such information needs to be considered concurrently with the medical and psychiatric evaluation of the patient. Unfortunately time constraints truncate this process and HE can limit a patients input. In the UK, the National Health Service Blood and Transfusion (NHSBT) service provides a list of absolute and relative contraindications to liver transplant<sup>30</sup>. Concurrent medical or psychiatric co-morbidity are deemed relevant if they are severe enough to affect the patient's prospect for

survival post-transplant or likelihood of compliance with medical therapy and outpatient clinic follow up. Medical contraindications include active sepsis, severe coexistent medical disease, progressive inotropic or ventilatory support or irreversible brain stem dysfunction. In terms of psycho-social disease, contraindications to transplantation include multiple previous episodes of self harm (>5), refractory or resistant mental illness, active intravenous drug use or polydrug or alcohol use in a severe and chaotic fashion and a consistently stated wish to die in the absence of established mental illness. In particular, predicting compliance with the intensive post-transplant immunosuppression and follow up regimen in those patients with psychiatric co-morbidity can be very difficult to assess within the time constraints available to assess the patient with ALF.

#### *Keeping patients alive on the transplant waiting list*

In view of significantly reduced survival time, patients with ALF are usually afforded priority for donated liver allocation in most countries. The US-ALF study group reported a median time from listing to transplant of one day<sup>2</sup> and Ichai reported a median listing to transplant time of 7.5 hours<sup>31</sup>. Despite this exceptional access to transplantation, the mortality of listed patients with ALF remains very high. A study from Kings College reported a 92% mortality rate of patients on the waiting list who did not receive a liver transplant<sup>32</sup>. In a large US study, 25% of all patients listed for transplantation for ALF died whilst awaiting a suitable graft<sup>15</sup>. In the Scottish cohort mortality on the transplant waiting list was higher in the APAP-ALF group (31.8%) compared with the non-APAP ALF group (15.7%)<sup>27</sup>. Ichai reported that 13.5% of patients listed for super-urgent OLT in France died or left the waiting list due to clinical deterioration<sup>31</sup>. The Kings College group report a significantly higher percentage of patients dying on the waiting list compared with the US and France, and this may be related to the higher percentage of patients listed with APAP-ALF. The Kings group also identified that in their cohort, a vasopressor requirement at time of listing was associated with a higher risk of failure to transplant and it is possible that this reflects listing of a sicker group of patients.

Keeping patients alive while awaiting a suitable donor organ is a significant challenge in the management of ALF. Critical care involvement is crucial. The intensive care management of these patients is complex and challenging. Although several guidelines exist<sup>24, 33</sup>, much remains to be determined with regards to the best evidence-based practice. ALF patients may develop overwhelming sepsis, multi-organ failure or irreversible cerebral edema with raised



intracranial pressure (ICP). Improvements in managing the ALF patient whilst awaiting a suitable graft include developments in renal support with a shift from using hemodialysis to continuous veno-venous hemofiltration (CVVH), and in particular, a better understanding of the pathogenesis and management of cerebral edema and raised intracranial pressure (ICP) in ALF which is discussed in more detail in the supplementary material.

### *De-listing*

Clearly, if a patient's condition deteriorates such that the outcome post-transplant was deemed futile, then that patient should be removed from the waiting list. However, futility is a vaguely defined concept and at present there are no validated criteria to assist in the decision making process. O'Grady has proposed a list of factors which might be utilized when deciding to proceed with transplant, when to pause and consider the benefit, and when to abandon the planned transplant<sup>34</sup>. 'Pausing' is suggested when patients show sustained improvement of prognostic criteria without general clinical deterioration, in those with APAP-ALF who do not have grade 3-4 HE or in whom severe acidosis or elevated lactate responds rapidly to resuscitation, and if the allocated graft is considered 'marginal.' Situations in which the planned transplant might be abandoned include rapidly escalating inotrope requirements, invasive fungal infection and objective evidence of brainstem death. Untreated infection or progressive infection despite 48 hours of appropriate antimicrobial therapy and clinically significant ARDS (FiO<sub>2</sub> >0.8) should also be considered a contraindication to transplant. Validated criteria assessing futility would be an extremely useful clinical tool. However until these are available individual decisions will continue to be made depending upon expert bedside assessment and dynamic clinical data.

Currently, no data or prediction models exist to facilitate clinical decision making in delisting patients because of clinical improvement. Potential delisting criteria in the setting of clinical improvement might include; reversal of HE, weaning from vasopressor support and recovery of renal function<sup>11</sup>. Timely delisting (when appropriate) should be considered equally as important in the patients clinical course as timely listing, to ensure maximum patient benefit and appropriate utilization of scarce donor organs.

### *Post-operative outcomes*

Immediate outcomes after emergency OLT for ALF are improving, but have not yet reached those reported following elective OLT. Liver transplantation for ALF is characterised by a relatively high early post-operative mortality, with the majority of deaths occurring in the

first 90 days after transplant<sup>35</sup>. For patients transplanted for ALF, 90-day mortality was higher in the UK (24.9%) versus the US (18.2%), and was higher than that reported with patients transplanted for CLD (UK 9.4% versus US 8.0%)<sup>36</sup>. Data from the European Liver Transplant Registry reported that 1-year survival for ALF after OLT is around 10% lower than that for elective transplantation<sup>35</sup>. However, overall outcomes have improved and 3-year patient survival can now exceed 75%. 5-year mortality of patients transplanted for ALF in the UK and US is 34.1% and 29.1% respectively, versus rates of 27.1% and 28.3% for those transplanted for CLD<sup>36</sup>. Patients transplanted for APAP and viral related ALF have better post-transplant outcomes than those transplanted for AIH and DILI-ALF<sup>2</sup>.

The recent UK Liver Transplant Audit<sup>37</sup> identified factors associated with increased risk of post-transplant mortality. These included older age of recipient, recipient ethnicity, requirement for pre-transplant renal support and the use of segmental/'split' grafts. High donor BMI is a predictor of recipient death post-transplant, presumably related to graft steatosis. Other potential risk factors for post-operative mortality or graft loss include donor age >60, male gender and the use of an ABO incompatible graft<sup>35</sup>. Recipient BMI and lowest recipient pH prior to transplantation have also been shown to be associated with poorer outcome post-transplantation<sup>38</sup>.

Over the preceding years, there has been increasing use of so called 'marginal donors' and alternative forms of liver transplantation to increase the donor pool for those listed for emergency OLT. ABO incompatible grafts have been used the setting of ALF with less favourable outcomes; 1-year survival is between 30 and 60%<sup>39</sup> with ABO mismatching an independent risk factor for graft loss and death at 3 and 12 months<sup>35</sup>.

Auxiliary liver grafting has been proposed as a temporising measure, either till native liver function recovers or formal transplantation occurs. This technique retains recipient liver and uses a partial right or left lobe of donor liver graft as a means of providing temporary liver support. Once native liver recovery occurs immunosuppression can be withdrawn with resultant shrinkage of the donor liver; this typically occurs within 1 to 3 years post OLT in 70% of patients<sup>34</sup>. Survival rates following auxiliary transplant have been reported to be 60-65%<sup>40</sup>. Experience of this transplant option is limited, accounting for only 2% of liver transplants in Europe between 1999 and 2009<sup>35</sup>, but this remains an exciting and attractive option worthy of further exploration as it negates the need for long term immunosuppression.

Living donor liver transplant (LDLT) may reduce waiting times for those patients with ALF who require an organ urgently, and is of particular importance in certain areas of the world. In Japan, more than 98% of patients transplanted for ALF underwent LDLT<sup>41</sup>. Interestingly, the median time to transplant from the onset of encephalopathy was 4 days, compared with 1 day in the US taking into account all donor types. One-year survival following adult to adult LDLT for all etiologies in the US was 81%<sup>42</sup>. In Japan, 1-, 5- and 10-year survival rates following LDLT for ALF are 79%, 74% and 73% respectively<sup>43</sup>. One major issue with the use of LDLT is the need for rapid yet thorough donor evaluation. One American group reported the outcomes of seven patients undergoing LDLT for ALF<sup>44</sup>. Donor work up was expedited and completed in a median of 24 hours. There was no significant difference in patients undergoing live or deceased donor transplantation in terms of post-operative complications, 1-, 3- and 5-year graft and patient survival. No severe donor complications were reported. LDLT may be a viable option to meet organ demand if the assessment process can be expedited with the process remaining thorough and complete without donor coercion. Larger studies with long-term follow up periods are required before this practice is more widely adopted.

There is limited experience of the use of donation after cardiac death (DCD) grafts in patients with ALF. In the US, the number of DCD transplants performed for all indications has steadily increased over time; however data suggest inferior liver graft survival for organs retrieved from DCD donors versus DBD (donation after brain death) donors in a cohort of patients including those with ALF<sup>45</sup>.

#### *Longer term outcomes following spontaneous survival of ALF*

In ALF, the presumption is that if the patient is supported long enough, the liver is capable of complete regeneration and the patient returns to normal health with no long-term adverse health sequelae. However, recent studies have challenged this presumption. Studies from the USA and Denmark suggest that survival and quality of life of patients recovering spontaneously from ALF are reduced compared with the general population or liver transplant recipients<sup>46-48</sup>.

#### *Long term health care outcomes following liver transplantation for ALF*

The available data would suggest that quality of life is worse in those transplanted for ALF (in particular APAP-ALF) compared with those transplanted for CLD and hepatocellular carcinoma<sup>49</sup>. In the transplanted APAP-ALF cohort, there are later problems with

psychosocial morbidity, medication compliance and clinic attendance. Anxiety symptoms have been reported in 33.2% and depression in 16.7% of APAP-ALF transplanted patients with ongoing social/psychiatric issues in 35%<sup>49, 50</sup>. The incidence of psychiatric disease and 30-day mortality is increased in patients with APAP-ALF compared with non-APAP ALF and CLD<sup>51</sup>. In addition, adherence to follow up and compliance with immunosuppression is reduced in the APAP-ALF group. These social problems translate into a 10 times higher incidence of death and graft failure in the APAP-ALF cohort compared with other etiologies<sup>35</sup>. A higher incidence of suicide in the APAP-ALF group occurs, with 57% of suicides within 12 months of transplantation<sup>35</sup>. These data highlight the difficulty in identifying suitable patients for OLT and developing health-care structures to provide longer-term support, particularly in the APAP cohort. Larger scale, long-term studies are necessary to investigate health care utilisation and outcomes in survivors of ALF (with and without transplantation), and to ensure the health care needs of this cohort are met.

#### *Alternatives to transplant*

Alternatives to liver transplant are urgently needed to fill the worldwide gap between supply and demand for donated organs. Potential alternatives include liver support systems, cell transplantation and liver tissue engineering, and such alternatives to transplant should be a major 'future direction' in managing the patient with ALF. This is a highly specialised, rapidly developing field, with several recently published reviews<sup>52-54</sup>. Potential alternative to transplantation are discussed individually in the supplementary text.

#### *Future Directions and Conclusions*

There is little doubt that earlier recognition of ALF and improvements in medical and intensive care management have improved outcomes for patients with ALF. Whilst the donor organ pool is currently limited, attempts are being made to expand the pool by utilising marginal donors and alternatives such as auxiliary and living donor transplant. A recent paper by Bernal<sup>55</sup> posed the question could ALF be a curable disease by 2024? To achieve this lofty goal, a number of factors need to be addressed in the next 10 years. Initially, a universally accepted definition of ALF must be established, to facilitate consistent and standardized research and clinical management of these patients. Further study of the pathogenesis and trajectory of disease is required to accurately and promptly define individual patient outcomes and identify new therapeutic targets with the aim of reducing the percentage of these patients who require emergency OLT. Furthermore, developments in the alternatives to

liver transplantation have the potential to limit the need for emergency liver transplantation and redirect donated organs for patients with chronic liver disease and cancer.

Accepted Article

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Table 1. UK registration criteria for super-urgent liver transplantation

CATEGORY	ETIOLOGY	CRITERIA
1	Acetaminophen	pH<7.25 more than 24 hours after overdose and after fluid resuscitation
2	Acetaminophen	Co-existing PT>100 seconds or INR>6.5 and serum creatinine >300umol/L or anuria, and grade 3-4 encephalopathy
3	Acetaminophen	Significant liver injury and coagulopathy following exclusion of other causes of hyperlactatemia after adequate fluid resuscitation: arterial lactate >5mmol/L on admission and >4mmol/L 24 hours later in presence of clinical HE
4	Acetaminophen	2 of the 3 criteria from category 2 with clinical evidence of deterioration (e.g. increased ICP, FiO <sub>2</sub> >50%, increasing inotrope requirements) in the absence of clinical sepsis
5	Favorable non-acetaminophen (e.g. viral hepatitis, cocaine)	The presence of clinical HE is mandatory and: PT>100 seconds or INR >6.5, or any 3 from the following: age>40

		or <10 years; PT>50 seconds or INR >3.5; any grade of HE with jaundice to encephalopathy time >7 days, serum bilirubin >300umol/L
6	Unfavorable non-acetaminophen (e.g. indeterminate ALF, DILI)	a) PT >100 seconds or INR>6.5 or b) in the absence of HE then INR >2 after vitamin K repletion is mandatory and any 2 from the following: age >40 or <10 years; PT >50 seconds or INR>3.5; if HE is present the jaundice to encephalopathy time >7 days; serum bilirubin >300umol/L
7	Acute Wilson disease or Budd-Chiari syndrome	A combination of coagulopathy and any grade of encephalopathy

## SUPPLEMENTAL MATERIAL

### *Non-transplant management options of individual conditions.*

#### Ischemic hepatitis

In ischemic or hypoxic hepatitis, the cornerstone of management is cardiovascular support and resuscitative measures. OLT is rarely indicated in ischemic hepatitis, or indeed feasible in view of the frequent presence of significant cardiorespiratory co-morbidity with high frequency of death from multiorgan failure reported<sup>1</sup>. In critically ill patients with ischemic hepatitis, statin therapy prior to critical care admission may be protective<sup>2</sup>.

#### Pregnancy-related ALF

ALF occurring during pregnancy as a result of AFLP or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) requires early delivery of the fetus, with good outcomes reported following delivery<sup>3, 4</sup>. However, postpartum deterioration can occur and transplantation may still be required if the liver failure does not resolve promptly after delivery<sup>3</sup>. Specifically in AFLP, it has been suggested that transplantation should be reserved for those with hepatic rupture complicated by necrosis, HE, severe metabolic acidosis and worsening coagulopathy<sup>5</sup>.

#### Viral hepatitis

For patients with ALF secondary to hepatitis B, treatment with nucleos(t)ide analogues should be considered. However, evidence of efficacy is equivocal<sup>6</sup>. Emerging data suggests ribavirin treatment is effective in cases of acute HEV infection<sup>7</sup>. Rarely, ALF may be caused by other viruses such as herpes virus or varicella zoster, and treatment with IV acyclovir should be started immediately<sup>8</sup>.

#### Wilson Disease

ALF due to Wilson disease is considered universally fatal and emergency OLT is the only proven therapeutic option for this disease process, even though liver cirrhosis is present. In those without HE, treatment with penicillamine or trientine may be tried in the first instance<sup>9</sup>.

#### Autoimmune Hepatitis

In patients with severe ALI due to autoimmune hepatitis (AIH) the decision regarding steroid therapy can be challenging, balancing the potential for recovery with the risk of sepsis in patients already with increased risk of infection. Ichai described 16 patients presenting with acute, severe or fulminant AIH, in whom 10 cases proceeded to transplantation despite steroid treatment<sup>10</sup>. Severe septic complications were noted in three treated patients. More

recently a retrospective study<sup>11</sup> identified a subset of patients with AIH-ALF with an initial MELD <27 and low grade HE that benefited from corticosteroids, an observation in keeping with AASLD recommendations<sup>3</sup>. Steroid use should therefore be avoided in AIH-ALF with advanced HE due to the risk of sepsis, worsening clinical condition and delay in consideration of OLT.

#### DILI

Steroids may also have a role in the management of DILI, in particular in cases where drug hypersensitivity such as the 'drug rash with eosinophilia and systemic symptoms' (DRESS) syndrome or an autoimmune reaction is implicated<sup>12</sup>.

#### Budd-Chiari Syndrome

ALF due to Budd-Chiari syndrome can respond to venous decompression via transjugular intra-hepatic portosystemic shunt (TIPSS) or hepatic vein stenting<sup>13</sup>, suggesting that OLT should be considered only in those patients who cannot be managed by TIPSS. Larger and longer term studies are required to clarify the best algorithm for the management of fulminant presentations of Budd-Chiari syndrome.

#### Alcoholic hepatitis

Alcoholic hepatitis is not usually considered a form of ALF, although when severe many features are similar, and there are few evidence-based medical therapies available. Early liver transplantation for severe alcoholic hepatitis remains a controversial issue. In a small group of patients (n=26) who were non-responders to steroids as assessed by the Lille score, early liver transplantation was associated with a significantly higher 6-month survival rate, and this benefit was maintained through 2 years of follow up<sup>14</sup>. Three of these patients returned to drinking alcohol. Reluctance to adopt this approach more widely relates to fears over harmful alcoholic recidivism, the fact that patients have not demonstrated their ability to gain control over their disease, and public perception that these patients may be less deserving of a transplant than other patients<sup>15</sup>.

#### *Development of infection and the Systemic Inflammatory Response Syndrome (SIRS)*

Developing infection and/or a SIRS response (two or more of: temperature <36<sup>0</sup>C or >38<sup>0</sup>C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO<sub>2</sub> <4.3kPa and leucocyte count <4x10<sup>9</sup>/L or >12x10<sup>9</sup>/L) and resultant multi-organ failure limit hepatic regeneration and reduce survival. However, no survival benefit has been shown with the use of prophylactic antimicrobials in ALF<sup>16, 17</sup>. The AASLD Position Paper<sup>3</sup> recommends that

periodic surveillance cultures are taken to identify infection early and that antibiotic treatment should be commenced at the earliest sign of active infection or deterioration, defined as progression to high grade HE or elements of SIRS.

Active infection can be difficult to diagnose as a SIRS response is frequently associated with ALF without infection. Rolando initially reported the frequent presence of SIRS in patients with ALF secondary to a variety of etiologies<sup>17</sup>. Overall 58.6% of patients developed a SIRS response and even in the absence of infection SIRS on admission was associated with a more critical illness, subsequent worsening of HE and death. These data have been reproduced by a number of different groups<sup>16, 18</sup>. Associated with the SIRS, a compensatory anti-inflammatory response syndrome (CARS) has also been implicated in the pathogenesis of multiorgan failure in ALF<sup>19</sup>. CARS is defined by persistently elevated levels of anti-inflammatory cytokines and impairment in cellular immune function. A pathological CARS has been reported in patients with ALF, characterised by excessive immunosuppression, functional monocyte deactivation, and increased predisposition to infection. Understanding the pathogenesis of SIRS and CARS in ALF might lead to novel therapies that reduce or prevent the high mortality related to infection in this condition.

#### *Assessing prognosis and listing for transplant*

The KCC were initially proposed by O'Grady in 1989 and were derived from a cohort of almost 600 patients<sup>20</sup>. All patients had Grade 3 or 4 HE, representing the most severe cases of ALF. These criteria differentiated between APAP and non-APAP etiologies. The KCC have been consistently shown to have a high degree of specificity, but a reduced sensitivity<sup>21, 22, 23</sup> (Supplementary Table 1). The KCC for APAP were later updated to include arterial lactate. Bernal<sup>24</sup> measured arterial blood lactate early and after fluid resuscitation in patients with APAP-ALF. Combined early and post-resuscitative lactate concentrations had similar predictive ability to standard KCC, but identified non-survivors earlier in their clinical course. Importantly with the observed increase in staggered APAP overdose in the UK is the observation that the KCC has reduced sensitivity in predicting outcome in this type of overdose pattern compared with single time point overdose (77.6% versus 89.9% respectively)<sup>25</sup>. A recent systematic review identified that the original KCC for APAP-ALF had a pooled sensitivity of 58.2% and specificity of 94.6% with a diagnostic odds ratio (DOR) of 27.7<sup>21</sup>. DOR is a measure of effectiveness of a test, defined as the ratio of the odds of the test being positive if the subject has the disease relative to the odds of the test being

positive if the subject does not have the disease; a large DOR is indicative of good test performance. In the UK, the criteria for listing patients with APAP-ALF for emergency OLT on the basis of arterial lactate has also recently been reviewed and modified<sup>26</sup>. Patients with APAP-ALF are now listed for OLT on the basis of both an arterial lactate >5mmol/L on admission and >4mmol/L 24 hours later in the presence of clinical HE.

McPhail<sup>22</sup> performed a meta-analysis of the performance of the KCC in predicting outcomes of patients with non-APAP ALF. Summary sensitivity was 68% with a specificity of 82% and DOR of 12.6. Importantly, this study identified that sensitivity was reduced in studies published later than 1995 (58%) compared with studies published earlier than 1995 (85%), with an associated fall in DOR over time. These results suggest that the performance of the KCC has deteriorated over time, at least in the non-APAP cohort, and that as the trajectory of the clinical course of the ALF patient is changing, the criteria need updating and further validation studies undertaken.

The Clichy criteria<sup>27</sup> were developed in France and are used predominantly in Northern Europe. These criteria were derived from a cohort of patients with ALF secondary to hepatitis B, and therefore may not be applicable to patients with non-viral etiologies. This scoring system is based upon the presence of HE and Factor V levels. Factor V measurement is not available in many countries, again limiting general application of these criteria. Yantorno reported that in adult patients with ALF, the Clichy criteria had a better positive predictive value (PPV) compared with KCC (87% versus 65% respectively), but a lower negative predictive value (67% versus 83% respectively)<sup>28</sup>. More recently Ichai has identified that the performance of the Clichy criteria could be improved if APAP-ALF and non-APAP ALF were differentiated, and if serum bilirubin and creatinine clearance were incorporated<sup>29</sup>. Unfortunately, as currently applied the Clichy criteria appear to have a limited prognostic capacity.

MELD was designed to estimate post-procedural mortality in cirrhotic patients undergoing TIPSS and has been widely evaluated in predicting mortality in those with chronic liver disease. Several studies have investigated the predictive power of MELD in patients with ALF. Kremers observed survival was negatively correlated with MELD in patients with non-APAP ALF<sup>30</sup>. Others have reported a MELD score >35 predicted mortality with a sensitivity of 86% and specificity of 75% in non-APAP ALF<sup>31</sup>. In APAP-ALF MELD was significantly higher in patients with HE, but did not perform any better than the KCC in predicting death<sup>32</sup>.



In a direct comparison of the prognostic accuracy of KCC, Clichy and MELD in adults with ALF, MELD was superior<sup>28</sup>. However, the authors recognised that this was a single center study with limited numbers and the most frequent cause of ALF was AIH; therefore the reported utility of MELD may not be generally applicable to other populations and further studies are required.

The role and utility of the widely used prognostic scoring systems may differ according to etiology of ALF. A recent meta-analysis identified that KCC more accurately predicted hospital mortality in APAP-ALF, whereas MELD more accurately predicted mortality in non-APAP ALF<sup>33</sup>. Within APAP-ALF, the performance of the KCC appears to vary with overdose pattern<sup>25</sup>. A few disease specific prognostic models for etiologies other than APAP poisoning have been reported, but generally have yet to be validated in larger and alternative ALF cohorts.

Several new scoring systems and prognostic biomarkers have been described, including the use of CT liver volume<sup>34, 35</sup> and thyroid hormone levels<sup>36</sup>. (Supplementary Table 2<sup>23, 34-43</sup>).

However, a systematic review of new models highlighted methodological and reporting limitations<sup>44</sup>. New prognostic models with high sensitivity and specificity are urgently needed. Increasing the sensitivity of prognostic scoring systems favours the individual patient, and improving the specificity would allow targeting of limited organs to those most likely to benefit. The ideal prognostic model should be highly sensitive and specific, with ease and rapidity of clinical application. The prognostic marker or scoring system should utilize readily available validated variables that could be dynamically applied to reflect the speed with which the clinical condition can evolve. Further multicenter studies assessing new scoring systems and adapting current prognostic systems with newly identified biomarkers are urgently required.

#### *Development and Management of Cerebral Edema (CE)*

CE is one of the most devastating complications of ALF as it may lead to the development of intracranial hypertension (ICH) and death. CE is rarely reported in patients with chronic liver disease, even in those with acute decompensation or acute on chronic liver failure. Up to 25% of ALF patients will develop CE, with CE occurring in up to 80% of patients with grade IV HE<sup>45</sup>. It was recently reported that the proportion of patients with ICH fell from 76% in 1984-1988 to 20% in 2004-2008, with 50% reduction in associated mortality<sup>46</sup>. Evolution of

therapies over the years such as use of NAC, antibiotic therapy and CVVH and earlier patient presentation were speculated to have modified potential factors in the pathogenesis of ICH.

The pathophysiology of CE in ALF is complex but now more completely understood<sup>47</sup> occurring as a consequence of vasodilatation of cerebral arterioles and neuroinflammation from a direct interaction between microglia and ammonia. An impaired urea cycle as a result of hepatocyte loss results in rising blood ammonia concentration. Hyperammonemia causes increased synthesis and accumulation of glutamine in astrocytes and cellular swelling. Arterial ammonia concentration is an independent risk factor for the development of higher grade HE and ICH, with an ammonia level  $>100\mu\text{mol/L}$  predicting the onset of severe HE with 70% accuracy<sup>48</sup>. Elevated arterial ammonia is also associated with a greater likelihood of death from brain herniation<sup>49</sup>.

Reductions in cerebral perfusion pressure (CPP) are associated with a high risk of ischemic brain injury. ICP monitoring allows earlier detection and management of elevated ICP and assists decision making. However, ICP monitoring has recognized complications. The risk of intracranial hemorrhage is significant and can lead to disability and death. A previous study from the United States reported bleeding in 21% of cases<sup>50</sup>. More recently the outcomes of those undergoing ICP monitoring in 25 US centers have been reported<sup>51</sup>. Of a sub-group of 58 patients Vaquero described a 10% complication rate, all related to intracranial hemorrhage. In those listed for OLT and managed with ICP monitoring, the 30-day survival rate post-transplant was not significantly different between the monitored and un-monitored group. No information was available on the long-term neurological recovery of these patients and this is a field worthy of further exploration. Transcranial Doppler ultrasound is an alternative non-invasive method of monitoring cerebral hemodynamics, with limited studies assessing utility in ALF<sup>52, 53</sup>. There is no worldwide agreement on the best practice in ICP monitoring and treatment of CE, however the AASLD practice guidelines for ALF<sup>3, 54</sup> advise that ICP monitoring should be utilized in patients with high grade HE, in centres with experience in ICP monitoring and in patients who are awaiting and undergoing OLT. This is another area worthy of future research.

Osmotic therapy with mannitol is recommended as first line therapy for raised ICP, having been shown in small studies to correct discrete episodes in patients with ALF<sup>54, 55</sup>. Induced hypernatremia (serum sodium 145-155 $\mu\text{mol/L}$ ) with hypertonic saline has also been shown to be effective<sup>56</sup>. Short acting barbiturates, therapeutic hypothermia (TH) and indomethacin are utilized as second-line measures to control ICP. In animal models of ALF, TH has been

shown to prevent development of CE<sup>57</sup>. However, a recent multicenter retrospective cohort analysis reported that TH did not have a significant effect on 21-day survival or transplant-free survival in humans<sup>58</sup>. In this study, TH was not associated with increased bleeding risk or infection. Further prospective studies would be useful to clarify if TH could have a role in the management of patients with ALF, particularly for those who are deemed to be at high risk of developing CE whilst on the transplant waiting list, such as the young and those with APAP-ALF.

Ammonia is a key contributor in the pathogenesis of HE and ICH in ALF. Therapies directed at reducing or clearing ammonia could potentially reduce HE and prevent ICH. Plasmapheresis decreases arterial ammonia and may have effects on systemic immune and endothelial dysfunction by reducing the pro-inflammatory milieu<sup>59</sup>. Plasmapheresis in ALF has demonstrated improvements in HE and hemodynamic parameters, but with no definitive effect on survival<sup>60</sup>. However, a recent randomized controlled trial investigated high-volume plasma exchange (HVP) in patients with ALF; overall hospital survival was higher in those treated with HVP versus the control group (58.7% versus 47.8%), and the authors postulated that improved survival was as a result of effects on immune activation and multi-organ dysfunction<sup>61</sup>. CVVH has also been proposed as a method of reducing circulating ammonia concentrations, with one study including patients with ALF reporting a 22% reduction in mean arterial ammonia concentration over 24 hours of CVVH<sup>62</sup>. L-ornithine L-aspartate (LOLA) can also reduce circulating ammonia concentrations by increasing hepatic ammonia disposal and peripheral metabolism. However, a double-blind, randomized, placebo controlled trial reported that LOLA infusion did not lower ammonia or improve survival in ALF<sup>63</sup>.

### *Alternatives to Transplant*

#### *Liver support systems*

Extra-corporeal liver assist devices (biological and non-biological) remain largely experimental. Biological liver support systems incorporate living liver cells into a device with the aim of allowing both detoxification and hepatic synthetic functions. The HepatAssist (Alliqua Inc, Langhorne, PA, USA) system is perhaps the best known biological device and utilizes porcine hepatocytes within a dialysis cartridge. In a prospective, randomized controlled multicenter trial of the HepatAssist in patients with ALF and primary non-function there was a trend towards increasing survival in the device treated group<sup>64</sup>. When analyzed

for confounding factors, survival in the group of patients with ALF was significantly higher in the HepatAssist treated group compared with controls. The Extracorporeal Liver Assist Device (ELAD) utilizes cells derived from a human hepatoblastoma cell line. A clinical pilot controlled study of this system demonstrated a slightly higher rate of improvement in HE after 6 hours of treatment in the ELAD group, however no significant survival benefit was demonstrated<sup>65</sup>.

Non-biological liver support systems facilitate removal of toxins not cleared by the non-functioning liver, but do not replace the synthetic function of the liver as they do not contain any living cells. The Molecular Adsorbent Recirculating System (MARS, Gambro Americas, Lakewood, CO) and Plasma Separation Adsorption and Dialysis system (Prometheus, Fresenius Medical Care, Bad Homburg, Germany) have been the most frequently studied non-biological systems. However, no non-biological device has been demonstrated to reduce mortality in ALF, and further developmental work is required<sup>66, 67</sup>.

A systematic review evaluating the effect of biological and non-biological support systems in ALF and acute on chronic liver failure reported that non-biological support systems reduced mortality in acute on chronic liver failure, however neither biological nor non-biological systems impacted upon mortality in ALF<sup>68</sup>. A further systematic review and meta-analysis looking at survival following extracorporeal liver support (biological and non-biological) found that these systems significantly improved survival in ALF with a number needed to treat of 8, whereas no significant survival benefit was seen in patients with acute on chronic liver disease<sup>69</sup>. The data with regards to liver support systems are therefore conflicting and larger scale studies following further developmental work are urgently needed.

#### *Cell Therapy: Hepatocyte transplantation*

Hepatocyte transplantation aims to repopulate the liver with functional donor hepatocytes, injected either directly into the liver, or into the spleen from where they can migrate to the liver. Hepatocytes for transplantation are usually prepared from donor liver tissue not used for transplantation, and may therefore represent marginal graft tissue. In animal models of ALF, hepatocyte transplantation can improve survival<sup>70, 71</sup>. Translation of this apparent benefit to humans has been hampered by the availability of functional human hepatocytes and difficulty in resuscitating the cells following cryopreservation. A few pediatric case reports exist<sup>72</sup> but further research and technological advances are required before hepatocyte transplantation for ALF can be adopted into clinical practice in adults.

#### *Cell Therapy: Stem cell therapy*

Stem cells or stem cell derived hepatocytes are one potential solution to the shortage of viable hepatocytes. Ramanathan investigated the effect of stem cell derived hepatocyte-like cells in an animal model of ALF<sup>71</sup>. In rats transplanted with these cells, increased survival rates were observed along with evidence of albumin production. One of the main limitations of stem cell therapy in humans is the limited cell survival post-transplant. This may be related to insufficient resistance of the transplanted cells to oxidative and inflammatory stressors<sup>73</sup>. Stem cell therapy for ALF is certainly worthy of further investigation and hopefully in due course translation into therapy for human ALF.

#### *Liver Tissue Engineering and Bioprinting*

Bioengineering methods have been developed that allow for maintenance of the anatomical structure of an organ such as the liver and allow repopulation with hepatic cells which can form physiological contacts. 3D bioprinting is a recent advance in tissue engineering that allows construction of parenchymal organ structures, and raises the possibility of being able to print a functional artificial liver. 3D organ printing uses biofabrication techniques to build 3D spheroids via a layered approach. Robbins<sup>74</sup> introduced 3D hepatic tissue along with a primitive microanatomy of stellate cells and endothelial cells using the NovoGen MMX Bioprinter, with liver specific metabolic function lasting up to 135 hours. This technique is still in its infancy, but is an exciting development in its field.

#### *Stimulation of Regeneration*

Liver regeneration following injury plays a vital role in determining patient outcome, particularly with regards to APAP-induced liver injury. Timely stimulation of liver regeneration with factors such as vascular endothelial growth factor improves survival following APAP overdose in mice<sup>75</sup>. The role of macrophage colony stimulating factor (CSF1) in liver regeneration has also been studied<sup>76</sup>. In patients with APAP-ALF, low levels of CSF1 were associated with increased mortality, and in mice, administration of CSF1 promoted hepatic macrophage accumulation. CSF1 may be a new therapeutic target in ALF. Further human studies are urgently required to identify signalling pathways involved in liver regeneration, which may provide a new therapeutic target for the patient with ALF.

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SUPPLEMENTAL TABLES.

Supplemental Table 1. Summary of recent systematic review and studies assessing utility of KCC

	ETIOLOGY	SENSITIVITY	SPECIFICITY	POOLED DOR	AUC
Craig <sup>21</sup> Systematic review	APAP-ALF	58.2% (95% CI 53.1-63.3)	94.6% (95% CI 93.0-95.9)	27.7 (95% CI 9.2-83.5)	0.91 (95% CI 0.79-0.99)
McPhail <sup>22</sup> Meta-analysis	Non-APAP ALF	68% (95% CI 59-77)	82% (95% CI 75-88)	12.6 (95% CI 6.5-26.1)	-
Cholongitas <sup>23</sup> Retrospective analysis	APAP-ALF	47%	83%	-	0.65

Supplemental Table 2. Alternative scoring systems and biomarkers in ALF

Model/marker	Study	Outcome
<b>SOFA</b>	Cholangitas <sup>23</sup>	Performed better in predicting prognosis than KCC/MELD in APAP-ALF (SOFA AUC 0.79, KCC AUC 0.65)
	Craig <sup>37</sup>	Score > 7 during first 96 hours in APAP-ALF predictive of death/transplant (sensitivity 95%, specificity 76.9%)
<b>Gc-Globulin</b>	Schioldt <sup>38</sup>	Gc-Globulin levels significantly higher in ALF spontaneous survivors versus those who died/were transplanted (p 0.002)
	Antoniades <sup>39</sup>	Gc-Globulin levels significantly higher in ALF spontaneous survivors versus those who died/were transplanted (p 0.01)
<b>M-30</b>	Rutherford <sup>40</sup> (ALFSG)	ALFSG index (including log <sub>10</sub> M-30) (AUC 0.822) better at identifying patients likely to die/be transplanted than KCC (AUC 0.654) or MELD (AUC 0.704)
	Possamai <sup>41</sup>	Admission M30 levels significantly higher in ALF patients versus CLD and normal controls. Admission levels correlate with outcome (AUC 0.755)
	Craig <sup>42</sup>	Did not improve prognostication beyond KCC in APAP-ALF
<b>Thyroid hormone</b>	Anastasiou <sup>36</sup>	Significantly higher TSH, T4 and T3 levels in ALF spontaneous survivors versus those who died/underwent transplantation
<b>CT liver volume</b>	Yamagishi <sup>34</sup>	CT-measured Estimated Liver Volume/Standard Liver Volume higher on day 0 and 5 in ALF survivors compared with those who died or underwent transplantation
	Shakil <sup>35</sup>	CT liver volume <1000mls and/or parenchymal necrosis >50% indicative of a poor prognosis
	Yamagishi <sup>43</sup>	CT liver volume (CTLV)/standard liver volume (SLV) ratio <0.80 had a 75.6% sensitivity and 92.3% specificity for death