Review

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Acute liver failure: A curable disease by 2024?

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Summary

Over the last three decades acute liver failure (ALF) has been transformed from a rare and poorly understood condition with a near universally fatal outcome, to one with a well characterized phenotype and disease course. Complex critical care protocols are now applied and emergency liver transplantation (ELT) is an established treatment option. These improvements in care are such that the majority of patients may now be expected to survive (Fig. 1). Key features of the condition have changed dramatically over time, with a remarkable fall in the incidence of cerebral edema and intracranial hypertension, a much feared complication. In this review, we summarize the current understanding of key aspects of the classification, pathophysiology and management of ALF, and discuss the foreseeable challenges that will need to be addressed for further improvements to be achieved.

Acute liver failure: Phenotype, epidemiology and outcome

Acute liver failure (ALF) was initially defined nearly 50 years ago as the simultaneous appearance of hepatic encephalopathy and coagulation defects in the setting of an acute liver insult of any kind and in the absence of pre-existing liver disease [1]. Over the years, definitions have varied in regard to duration from time of onset to signs of liver failure, and each etiology is characterized by a relatively specific latency. A remarkably consistent central pattern of clinical signs and symptoms characterizes all causes of ALF, regardless of etiology when severe liver injury evolves over days or weeks: prolonged prothrombin time/INR (PT/INR), decline in mental function, peripheral vasodilation, features of the systemic inflammatory response syndrome, and ultimately multi-organ failure [2]. This section will emphasize the role of etiology in epidemiology and outcomes; despite the relatively uniform clinical presentation, the different causes of ALF are associated with remarkably different outcomes [3]. Thus, the outcome is defined by the etiology, which must be determined for prognostic assessment and where possible, to apply appropriate cause-specific therapy.

Role of etiologies worldwide

Over the past half century, the relative frequency of causes of ALF has evolved, with hepatitis A and B declining in incidence, and paracetamol (acetaminophen) increasing, at least in Western Europe and the United States [4]. The differences in etiology between developing and developed countries are well characterized, Europe and the United States feature a high incidence of paracetamol toxicity leading to ALF along with drug-induced liver injury due to prescription agents, less common but equally as important. By contrast, South Asia and Hong Kong have a higher incidence of hepatitis viruses, specifically hepatitis E in Pakistan and hepatitis B in Hong Kong, as well as in Australia, with fewer cases of drug-induced liver injury observed at least in the developing world [5,6].

Data from the United States collected over a 17-year period highlights the critical effect of paracetamol usage on ALF over this time, comprising nearly half of all cases over this long period (Fig. 2). In parallel to paracetamol overdoses, idiosyncratic drug-induced liver injury is one of the most common discernible causes, whilst indeterminate etiology (cause not discernible after extensive evaluation) continues to be a sizable patient group. In the United Kingdom paracetamol remains the predominant etiology of ALF, but an exponential rise in severe poisoning was effectively controlled by the restriction imposed on sales of the drug in 1998 [7].

Keywords: Acute liver failure; Transplantation; Cerebral edema; Ammonia.
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Abbreviations: ALF, Acute Liver Failure; ELT, Emergency Liver Transplantation; ICH, Intracranial Hypertension; INR, international normalized ratio; NAC, *N*-acetylcysteine; ECLAD, Extracorporeal liver assist devices; AOCLF, Acute on Chronic Liver Failure; MARS, Molecular adsorbent recirculating system; RCT, Randomized controlled trial; BBB, Blood brain barrier; GS, Glutamine Synthase; TCA, Tricarboxylic acid; ATP, Adenosine Triphosphate; GTP, Guanosine Triphosphate; MPT, Mitochondrial permeability transition; RRT, Renal replacement therapy; ICP, Intracranial Pressure; NSAID, Non-steroidal anti-inflammatory drug; KCH, Kings College Hospital; CT, Computed Tomography.

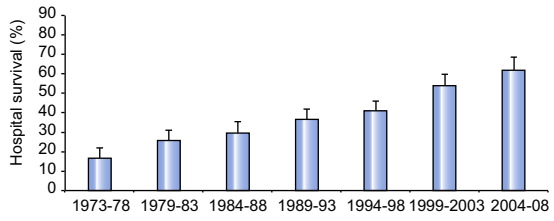

Fig. 1. Hospital survival for patients with ALF with encephalopathy of grade 3 and above, King's College Hospital, UK 1973–2008, (N = 2095). Error bars are 95% confidence intervals. p <0.0001. Source: Bernal *et al.* J Hepatol 2013; 59:74–80 [18].

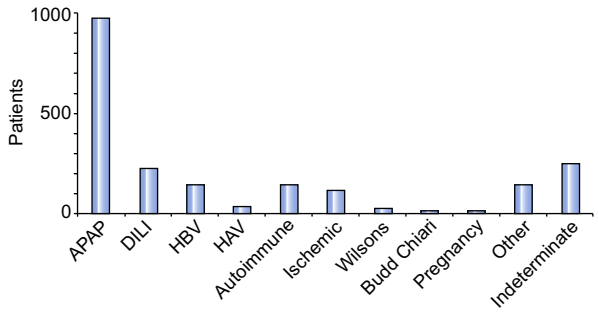

Fig. 2. Etiology of ALF in the USA: US ALFSG Adult Registry 1998–2014, (N = 2102). APAP, paracetamol; DILI, non-paracetamol drug-induced liver injury; HBV, Hepatitis B virus; HAV, Hepatitis A infection. Source: US ALFSG unpublished data October 2014.

Duration of illness

Important in understanding the clinical features and prognosis in ALF is the relationship of injury pattern, determined by etiology, and course of illness and its duration [8]. Varying names have been applied but the terms hyperacute, acute and sub-acute are often used [8]. The period of active injury in paracetamol and ischemic cases may be measured in hours, and it is self-limited. With this overall pattern of illness (very short), there is rapid onset and offset, and a finite period of necrosis. These patients are characterized as having a 'hyperacute' pattern, and, in many cases, a rapid recovery despite massive multi-organ failure. This pattern differs greatly from most other forms of ALF, usually termed 'acute or sub-acute', wherein the pattern of injury evolves over 1–4 weeks, and is not self-limited, but long lasting. Drug-induced liver injury, hepatitis B, autoimmune hepatitis and most indeterminate cases will have a sub-acute pattern and a worse survival.

The liver tests results differs markedly, with the hyperacute patients characterized by low bilirubin levels and strikingly high aminotransferases, characteristic of cell necrosis as the primary pathogenetic mechanism (Table 1). By contrast, sub-acute patients have lower serum aminotransferases and higher serum bilirubin values, consequent upon a more gradual liver injury and thus longer time interval to reach a stage of ALF with severe hyperbilirubinemia. The pathogenic mechanisms likely vary among the etiologies, but apoptosis and activation of the adaptive immune response are important here.

Specific therapies

It follows that therapy where possible should be directed at the specific etiology [2,9]. However, once ALF ensues, liver damage may be established and it may be too late for specific therapies to be effective. For example, *N*-acetylcysteine (NAC) is the known antidote for paracetamol overdose, and is given even days after onset of injury despite uncertainty as to its efficacy when given late [10]. There is also uncertainty relating to the use of NAC for non-paracetamol liver injury. An apparent survival benefit from its use has been shown in early stage ALF for non-paracetamol etiologies, but not for those with advanced coma grades [11]. In most ALF settings, NAC appears to be safe and is administered because of possible, not certain, benefit once severe injury is already established [9]. Other agents of uncertain benefit include nucleoside analogues for hepatitis B, and corticosteroids for ALF resulting from autoimmune hepatitis; prolonged steroid use may predispose to infection and preclude definitive transplantation [12,13].

Conclusion

Establishing the correct etiologic diagnosis is vital for the management of ALF as it unfolds, on account that diagnosis impacts therapy choice as well as prognosis. Most prognostic scores include specification of etiology and/or time of illness [12,14]. Efforts are now underway to ensure that the etiology is correctly diagnosed in a timely fashion using measures beyond the usual hepatitis and autoimmune serologies, e.g., use of paracetamol-cys adduct measurements to confirm or deny that paracetamol is the cause of injury [15]. In some instances, the original diagnosis needs to be re-examined in this light.

Key Points

- Survival for patients with ALF has improved dramatically in the last three decades, reflecting advances in medical critical care and the use of transplantation
- Establishing the correct etiologic diagnosis remains vital to management of evolving ALF, since diagnosis impacts therapy choices as well as prognostic assessment
- Supportive medical care is most effective when commenced early, addressing all aspects of the multi-organ dysfunction and failure seen in ALF
- The incidence of cerebral edema and intra-cranial hypertension has fallen markedly over time and is likely related to earlier disease recognition and better initial treatment, control of body temperature, plasma tonicity, systemic hemodynamics and early use of renal replacement therapy
- Results for emergency liver transplantation in ALF have improved and in the long-term are close to those for an elective procedure. The sensitivity of prognostic criteria remains to be improved and makes for difficulties in transplant selection
- For paracetamol (acetaminophen) induced ALF, survival with medical care now approaches that for liver transplantation, raising questions of transplant benefit

Table 1. Cumulative demographic, laboratory and outcome data by etiology of ALF. ALFSG Adult Registry, USA 1998–2014, n = 2000.

	APAP n = 916	DILI n = 220	Indeterminate n = 245	HAV n = 36	HBV n = 142	All others n = 441
Age (median years)	37	46	39	49	43	45
Sex (% F)	76	69	59	44	44	71
Jaundice to coma (median days)	1	12	11	4	8	7
HE grade ≥3 (%)	53	35	48	56	52	38
ALT (median IU)	3773	640	865	2275	1649	681
Bilirubin (median μmol/L)	74	339	361	210	315	238
Transplanted (%)	9	40	42	33	39	32
Spontaneous survival (%)	66	24	22	50	21	31
Overall survival (%)	73	58	60	72	55	58

APAP, paracetamol; DILI, non-paracetamol drug-induced liver injury; HBV, hepatitis B virus; HAV, Hepatitis A infection; HE, hepatic encephalopathy. Source; ALFSG unpublished data October 2014.

Pathophysiology of encephalopathy and cerebral edema (CE); why has incidence of CE fallen?

The development of disordered brain function, manifested as hepatic encephalopathy, is a key element of the multisystem illness that accompanies ALF. In patients with advanced encephalopathy, CE may also evolve and cause death due to cerebral herniation [16,17]. Unexpectedly, the incidence of CE has declined markedly over the last three decades and in many centres it is now seen in fewer than a quarter of patients, even when high-grade encephalopathy is present [18,19] (Fig. 3A and B). This may reflect both improvements in preventative medical care and the consequences of the use of ELT, which rapidly restores liver function in those patients at most risk of CE. However, once CE has developed in ALF it is still associated with very poor survival and complex critical care management is required [2,18].

Pathophysiology

The pathophysiology of both hepatic encephalopathy and brain edema in ALF are multi-factorial and its better characterization may provide some explanation of the changes in incidence of CE and herniation (Fig. 4). Release of material from dying cells within the liver and a "spill-over" of pro-inflammatory mediators from the splanchnic area to the systemic circulation results in cardiovascular instability; resembling vasodilatory septic shock, with low systemic vascular resistance, high cardiac output and a low arterial blood pressure that result in a decline in cerebral perfusion pressure [2,20].

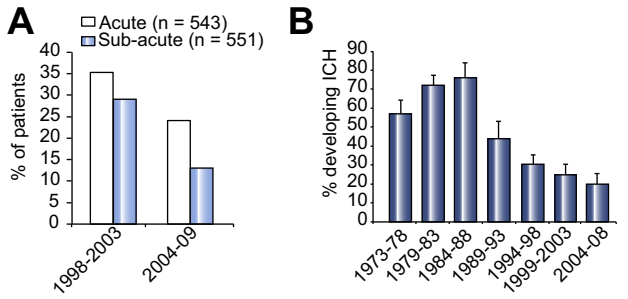

Fig. 3. Changing prevalence of cerebral edema (CE) in ALF. (A) Clinical evidence of CE in patients with ALF by presentation of illness. Japan 1998–2009, (N = 1094). Source: Oketani M *et al.*, Hepatol Res 2013;43:97–105 [19]. Acute <10 d, sub-acute 10 d-8 wk. (B) Clinical evidence of CE-related Intracranial Hypertension (ICH) in patients with ALF and encephalopathy of grade 3 and above, Kings College Hospital UK 1973–2008, (N = 1549). Error bars are 95% confidence intervals. p <0.0001. Source: Bernal *et al.* J Hepatol 2013; 59:74–80 [18].

This reduction in arterial pressure would normally not affect the brain due to a strict regulation of cerebral blood flow. This regulation is, however, absent in patients with ALF, and episodes of arterial hypotension may directly result in cerebral hypoperfusion and induce, or worsen CE [21]. Systemic inflammatory mediators may affect the brain by altering the cerebral endothelial function and may cross the blood–brain barrier (BBB) and induce CE through microglial activation [22]. However, the most important pathogenic factor for development of encephalopathy and CE is the release of ammonia from the failing liver due to a lack of urea synthesis. Experimental and clinical studies over the last three decades document that acute hyperammonemia specifically affects the brain, as ammonia easily crosses the BBB, and have characterized its role as a potent neurotoxin [23].

Once ammonia has crossed the BBB, glutamine synthetase (GS), primarily found in astrocytes, catalyses' glutamate to glutamine through utilization of ammonia. This process of detoxification results in the accumulation of glutamine that acts as an organic osmolyte and increases astrocyte volume, resulting in metabolic disturbances by a dysequilibrium of biochemical pathways promoting a shortage of glutamate. A decline in glutamate concentration can only partly be prevented by amination of α-ketoglutarate to glutamate but may, in severe persistent cases of hyperammonemia, result in substrate depletion of the tricarboxylic acid cycle where α-ketoglutarate is an essential metabolite. Furthermore, ammonia may inhibit two rate limiting enzymes; pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. The imminent substrate depletion and partial enzyme inhibition compromise overall oxidative metabolism and lead to depletion of energy-rich phosphate compounds (ATP and GTP) and accumulation of lactate [24–26]. In addition, ammonia both induces oxidative and nitrosative stress by formation of free radicals which may in turn result in mitochondrial permeability transition (MPT), i.e., a state with imminent "power failure" of the orchestrating astrocytes [23,24].

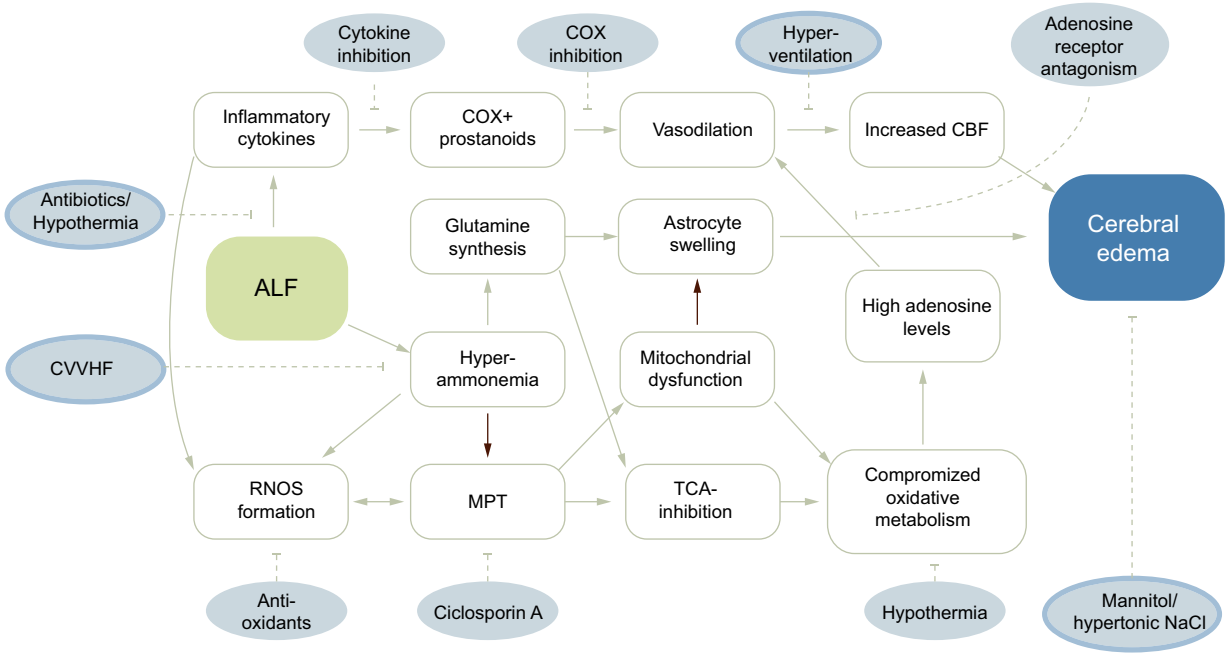

Fig. 4. An integrated model of the pathogenesis of cerebral edema (CE) in ALF. Potential interventions are depicted in light blue circles, and those in clinical use with darker blue outline. ALF, acute liver failure; CBF, cerebral blood flow; COX, cyclooxygenase; CVVHF, continuous venovenous hemofiltration; MPT, mitochondrial permeability transition; NaCl, saline; RNOS, reactive nitrogen and oxygen species; TCA, tricarboxylic acid; TNF, tumor necrosis factor. (Modified and reproduced with permission from authors and publisher: Bjerring PN *et al.* The brain in acute liver failure. Metab Brain Dis 2009; 24:5–14).

As a consequence of these processes water is taken up into the astrocytes and they swell. The compensatory mechanisms normally initiated to counteract astrocyte volume changes act through restoration of the osmotic balance between the intracellular and extracellular milieu, by the combined activation of chloride and potassium channels, and later by release of organic osmolytes including myo-inositol and taurine. These mechanisms are highly energy dependent and require optimal metabolic conditions to operate. Consequently the failure of the astrocytes "regulatory volume decrease" mechanism results in their swelling and leads to CE. The development of hyponatraemia, which is common in ALF, will only worsen such brain swelling as the associated fall in serum osmolality creates an osmolar gradient that favors water movement into the cells [2,27].

Approaches to neurological care

The complex interplay between changes in haemodynamics, immune response, ammonia trafficking, osmotic cell load, oxidative metabolism and plasma tonicity are all components that need to be considered when managing ALF patients to secure brain viability. To achieve this, restoration of circulating volume, prevention of sepsis, inotropic and vasopressor support, and sedation and mechanical ventilation are cornerstones in the management of these patients. The place of invasive intracranial pressure monitoring remains uncertain and controversial with little evidence to suggest clinical benefit, albeit with a low rate of complications [28]. Early initiation of continuous renal replacement therapy with or without addition of hypertonic saline may help to decrease the level of circulating ammonia and restore the normal osmotic gradient across the BBB by keeping the tonicity high [2]. Since systemic inflammation may result from a spill-over of pro-inflammatory mediators from the failing liver, total hepatectomy and the use of various liver assist devices as a bridge to transplantation have been utilized and reported to control brain edema, however such effects may relate to lowering of body temperature.

Lowering the body temperature slows down the rate of metabolic processes that are involved in development of CE, and the induction of mild hypothermia can be lifesaving in patients awaiting ELT [29]. It remains, however, unclear if ALF patients who are not liver transplantation candidates will benefit from this kind of intervention, with retrospective studies showing little evidence of improved survival [2,30]. A prospective randomized, controlled study of controlling intracranial pressure by lowering the body temperature prophylactively in ALF patients has been carried out and the final results are pending [31]. In ALF with manifesting intracranial hypertension, the anti-inflammatory non-steroidal anti-inflammatory drug (NSAID) indomethacin has been shown to prevent CE and further intracranial hypertension [32]. This effect is also seen after the administration of diclofenac, indicating that NSAIDs may be effective by blocking the cyclooxygenases. However, the prophylactic use of these NSAIDs in patients' needs further investigation as they may also induce renal dysfunction.

The role of glutamine-induced MPT in the development of clinically overt CE in ALF patients introduces the possibility of new therapeutic approaches in achieving neuroprotection by use of MPT-inhibitors such as L-histidin and cyclosporine [23]. There are indications that the use of hemofiltration, liver assist devices or plasma exchange may have a role in increasing ammonia clearance, and modulate the immune system and prevent development of multi-organ failure and brain edema [2,33].

Review

Medical management

Supportive care

The approach to medical supportive care delivered to patients with ALF must be comprehensive, addressing the multiple organ systems that may be involved. Certain etiologies of ALF have the potential for recovery through native liver regeneration and resolution of extra-hepatic organ failure. The overall aims of supportive care are thus to optimize conditions for hepatic regeneration, and to anticipate and prevent complications, whilst continually assessing native liver recovery and potential need for transplantation [2]. The success of these approaches to care are reflected in the progressive improvements seen in survival both with and without transplantation [18].

Where possible, potential precipitants should be actively treated as this may mitigate the severity of subsequent hepatic and extra-hepatic organ dysfunction or failure. These treatments, along with more generic supportive care, should commence as early as possible to maximize clinical benefit. The majority of patients with ALF are fluid depleted at presentation and require fluid resuscitation. The exception may be patients with hypoxic hepatitis, where fluid overload maybe a contributing factor to hepatic congestion and liver injury, necessitating venous off loading and inotropic support [34]. The fluid choice at initial presentation would normally be a crystalloid, with normal saline being the most frequently used solution. Despite marked perturbation of laboratory tests of coagulation, functional testing may reveal no major bleeding tendency or even a prothrombotic state. Loss of hepatic synthesis of procoagulant factors is paralleled by that of anticoagulants and thus a balanced hemostatic defect often exists [35]. Overt bleeding is uncommon and routine administration of coagulation factors is not indicated.

The level of monitoring required will depend upon the clinical situation and needs to be responsive to changing physiology. Patients with coagulopathy and encephalopathy or renal dysfunction should be monitored in a critical care environment with full access to invasive cardiovascular monitoring, alongside echocardiographic and ultrasound support to assess fluid responsiveness and requirement for vasoactive medication. Easy access to ventilatory support is required as encephalopathy may progress rapidly, with most centres intubating and ventilating those patients who develop anything more than low-grade encephalopathy.

Monitoring of arterial blood gases will allow tracking of sodium, chloride and lactate, close control of which is essential in the provision of optimal care. Sodium levels should be maintained at the high end of normal with aims between 145 and 150 mmol/L following development of high-grade encephalopathy [36]. Monitoring of lactate provides a composite assessment of production and clearance. Initial hyperlactataemia often relates usually to fluid depletion and is frequently reversible; subsequent lactate production is likely driven by catecholamine-induced muscle production alongside impaired liver clearance [37]. Sustained elevations in lactate after restoration of circulating volume provides important prognostic information and may help identify candidates for transplantation [38,39]. Magnesium and phosphate should be actively monitored and maintained in the normal range.

A systemic inflammatory response is a marker of significance reflecting severity of liver insult, development of extra-hepatic organ dysfunction and risk of death [40–42]. It may or may not be driven by sepsis; decision making in respect of antibiotic and antifungal medication should be undertaken on the basis of clinical assessment. Most patients with encephalopathy in association with coagulopathy or renal failure will be managed with antibiotics, often in combination with antifungal agents.

Renal dysfunction is common in ALF and may be poorly represented by the standard measures of creatinine or urea. In patients with ALF the role of the kidney in ammonia clearance becomes increasingly important and arterial ammonia levels should be closely monitored. Early institution of renal replacement therapy facilitates biochemical and temperature control, fluid balance and controls circulating ammonia levels. Clinically significant ammonia clearance can be achieved in adult patients with hyperammonaemia utilizing conventional continuous hemofiltration, with a clearance rate correlating closely with that of hemofiltration (Fig. 5) [43].

Management of the airway is required in those with high-grade encephalopathy or more rarely in the management of hypoxaemia [44]. Standard ventilator techniques should be undertaken to limit tidal volume and plateau pressure whilst ensuring normocarbia. Sedative agents would normally comprise intravenous propofol and an opiate.

Function of the gastro-intestinal tract is often impaired and pancreatitis should be excluded [45]. Enteral nutrition may be tolerated, and if instituted, arterial ammonia should be monitored as hyperammonemia may be triggered by moderate enteral protein loads in those patients with major acute hepatic insufficiency. If enteral nutrition is not tolerated later introduction of intravenous feeding may be considered [46]. Normoglycaemia should be monitored, and if not maintained 20% and 50% dextrose should be used to achieve normoglycaemia without causing hyponatraemia.

Extracorporeal liver support devices

Extracorporeal Liver Assist Devices (ECLAD) have long been sought as a means to temporarily replace lost liver function whilst awaiting definitive transplantation or native liver regeneration. However, despite decades of research and millions of euros of speculative investment, no device has yet been shown to be of definitive benefit to patients with ALF.

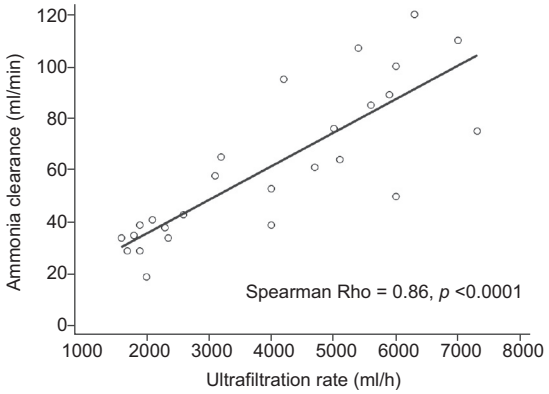

Fig. 5. Correlation between continuous venovenous hemofiltration ultrafiltration rate and ammonia clearance in patients with liver failure. Source: Slack AJ *et al.* Liver Int 2014:34:42–48 [43].

An effective ECLAD could be of great clinical utility in ALF: as discussed above, in some etiologies of disease, hepatic regenerative potential exists despite initially profound hepatic insufficiency. ECLAD could form a rapidly available 'off the shelf' device to stabilize hepatic function as an adjunct to other forms of supportive therapy. In doing so it might increase the proportion of patients surviving with medical management alone. When the threshold beyond which successful hepatic regeneration cannot occur has been crossed and transplantation is required, such devices could temporarily augment liver function and stabilize clinical condition whilst a graft is awaited.

These devices can be broadly categorized as biological or non-biological; the former seek to utilize the synthetic and detoxifying metabolic activity of human or non-human cells upon the blood or plasma of patients with ALF, and the latter is 'detoxification' through a variety of filtration or absorption mechanisms.

Some devices have shown initial promise with evidence of biochemical improvement and case series have suggested clinical benefit. In consequence, some devices have been in clinical use without definitive confirmation of efficacy; the rarity, severity and heterogeneity of ALF make it a uniquely difficult and expensive condition upon which to perform randomized clinical trials, particularly so when further complicated by the logistics of providing a complex and functional device at the point of need. Trials of some of these devices have now been performed in ALF but without definitive evidence of benefit.

The Molecular Adsorbent Recirculating System (MARS) device has been in use for both ALF and Acute on Chronic Liver Failure (AOCLF) in various configurations since 1993 and aims to remove toxic molecules through plasma dialysis across an albumin-porous exchange membrane and absorption into a series of binding columns. Its use in patients with liver failure is associated with biochemical improvements, though these may not be sustained [47]. An RCT in ALF has now been published: in a French multicentre study 102 patients fulfilling poor prognosis criteria were randomized to receive MARS therapy or standard of care; in those treated with MARS the median cumulative duration of therapy was 10 hours [33]. On both per-protocol and intention-to-treat analysis, and when stratified for etiology there was no significant differences in survival. Sixty-six percent of patients underwent ELT, at a median of 16 hours after randomization, curtailing the duration of treatment and making definitive confirmation of lack of efficacy impossible.

Biological devices present greater technical and logistical issues in their development and clinical application. Nonetheless, several generations of device have been developed and applied to patients over the last three decades – with only one relatively recent RCT [48]. This trial used the HepatAssist device which utilizes porcine hepatocytes in a bioreactor perfused with the patient's plasma. In a study of 171 patients with ALF or post transplantation primary graft non-function, the device showed no survival advantage over standard care on intention-to-treat analysis, though a post hoc assessment of patients with good prognosis etiologies gave some indications of improved survival [48].

A new generation of biological devices is shortly to begin clinical trials and may yet show the real practical benefits and improved patient outcome that current devices have failed to deliver. Other novel therapies also have promise, with initial reports of a RCT of High Volume Plasma Exchange suggesting a mortality benefit from its use [49].

Evolution of liver transplantation for ALF and issues of candidate selection

The introduction of ELT for the treatment of patients with ALF in the mid-1980s was a notable achievement and many desperately ill patients who would have previously died of the condition owe their lives to it. In the King's College Hospital (KCH) series of over 3300 patients with ALF, the overall survival rate in 2008, including those transplanted, was 62.2% compared with 16.7% in 1973 [18] (Fig. 1). Medical care has also improved and questions are now being raised as to the additional benefit of transplantation and of the criteria used in the selection of patients for transplantation.

Transplantation outcomes

ELT in such desperately sick patients would be expected to carry a high operative and post-operative complication rate and the recently published data of the European Liver Transplant Registry show just how survival results have improved, although 1 year survival is still around 10% less than for elective transplants (Fig. 6) [50]. Characteristically, the survival curve has an initial steep dip over the first 3 months reflecting operative and early post-operative complications and is then almost levelled, unlike that seen with cirrhosis or primary hepatocellular carcinoma where there is a steady decline due to recurrence of original disease or the effects of co-morbidity in an older age group. Because of the flat curve, the 5 and 10 year survival figures; of 75% and 72% for the last 5 year period analysed compare favourably with those for elective transplants. Independent risk factors for mortality comprise recipient age of >50 years, male gender, donor age >60 years and the use of incompatible or reduced sized graft. These risk factors can make a striking difference to first year mortality; 57% for a male more than 50 years old receiving an organ from a donor aged 60 years or more [50].

Clinical deterioration in ALF, particularly of the hyperacute category, can be extraordinarily rapid and survival is heavily dependent on time taken to obtain an organ. A study from the KCH group showed that of the 74 cases placed on the waiting list that did not get transplanted, 52 died before an organ became

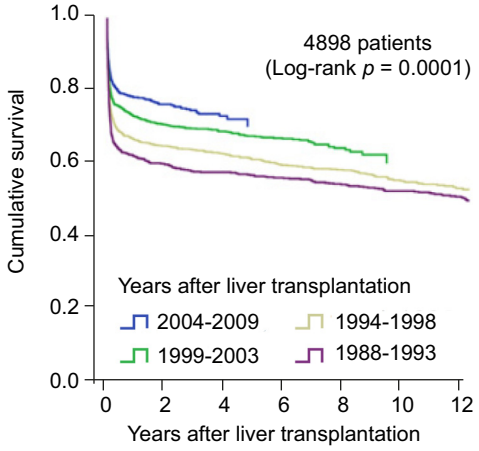

Fig. 6. Patient survival after liver transplantation for ALF, Europe 1988–2009. Source: Germani *et al.* J Hepatol 2012; 57:288–296 [50].

available and 15 became too ill for the transplant within a median of 2 days [51]. The importance of the prioritization in donor allocation accorded to ALF in most countries cannot be over stressed.

Prognostic and selection criteria

An important question is whether the better results from medical care alter the value of the criteria used in transplant selection and the overall transplant benefit. This is particularly so for the paracetamol hyperacute category of cases as O'Grady has recently discussed [52]. The overall hospital survival rate for paracetamol-related ALF and grade 3 or 4 encephalopathy in the KCH series was 66%; three-quarters of these patients had not received a liver transplant but still had a survival rate of 52%. A prospective study of 275 paracetamol-related ALF transplants carried out by the USA ALF group included 72 patients on the waiting list who had a survival rate of 73%, increasing to only 78% after liver transplantation [52].

Not only survival benefit but the quality of life after the transplant has to be considered. In the first of two recent studies, social problems post-transplant as a cause of death or graft failure including non-adherence to immunosuppression were nearly 10% higher in the paracetamol overdose cases than for other etiologies [50]. In the second study, the non-transplanted spontaneous survivors had the greatest decrease in quality of life with high rates of psychiatric disease and substance abuse raising further questions as to the appropriateness of ELT for this category of ALF [53].

The question of whether better medical care is altering the values of prognostic indices of long-established criteria used in transplant selection is a difficult one. The KCH Criteria first described in 1989 which has different modellings for paracetamol and non-paracetamol categories continue to be very widely used [14]. One recent addition is measurement of blood lactate, which at high levels proves to be an excellent prognostic marker of severe liver injury from paracetamol. Its specificity for both paracetamol and non-paracetamol cases as initially described was high, as shown by high positive predictive values of 95% and 100% respectively [54,39]. Negative predictive values, however, in the original series and subsequent studies are lower, indicating that for patients not fulfilling the criteria who were not therefore listed, there was still a significant chance of dying. The pooled meta-analysis of the KCH Criteria carried out in 2010 showed specificity to be high for paracetamol ALF at 95% [55], and less for the non-paracetamol category at 81% [56]. Sensitivity was relatively poor for both groups; 58% for paracetamol and 68% for non-paracetamol. Interestingly, sensitivity for the non-paracetamol group was found to be less in studies post 2005 as compared with earlier findings [56].

Not surprisingly, a number of other prognostic and scoring systems have been instigated with the desire to obtain more optimal sensitivity as well as retaining specificity. MELD was found to outperform KCH Criteria in 1 of 4 studies, and transplant selection based on SOFA and APACHE II scores was shown to be better than both of these [57,58]. The USA ALF Study Group reported that the addition of the apoptosis marker M30 of the CK18 molecule improved the sensitivity of the KCH Criteria to 86% but specificity was reduced to 65% [59]. Serial measurement of liver volumes on CT, comparing the 5 day result with that on admission, provided an objective index [60], and in another study the finding of a liver volume of less than 1000 ml had a predicted mortality of 97% [61]. The best approach almost certainly is a dynamic one, as utilized in the new assessment models developed in the UK and India [62,63]. The sequential daily assessment of prognostically important variables has shown predictive accuracy superior to the standard KCH Criteria [62,63].

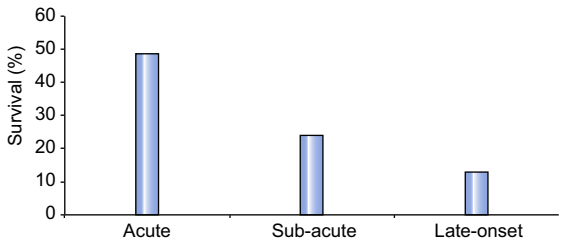

Fig. 7. Non-transplanted survival in patients with ALF by presentation of illness, Japan 2004–09 (N = 352). Disease onset to encephalopathy; Acute <10 days, Sub-acute 10 d-8 wk, Late onset 8–24 weeks. Source: Oketani M *et al.*, Hepatol Res 2013; 43:97–105 [19].

The indication for a transplant is clearer in the indeterminate, seronegative hepatitis or sub-acute liver failure category as medical care alone has so far not substantially improved the chances of spontaneous recovery (Fig. 7). A single centre experience showed excellent early and long-term survival figures for transplantation; 81% at 12 months and 73% at 5 years [64]. A high BMI for the donor was the most important predictor of death after transplantation, presumably related to steatosis of the graft. Most of the deaths in this group occur within the first 2 months from sepsis and multi-organ failure. A timely transplant which means an early decision on the need for it, is essential.

Conclusion

In conclusion, we have accumulated an extraordinary amount of knowledge about the pathophysiology of the main causes of ALF over the past 40 years. Gaps remain, particularly, for instance, in the late onset indeterminate category and more investigative research needs to be directed to this group of patients. Over the same 40 years we have seen extraordinary advances in patient care for what was once considered a uniformly fatal diagnosis. Improving survival rates even further will be dependent on gaining a better understanding of disease progression and the evolution of multi-organ failure. We need to refine and improve extracorporeal liver support which will give the time necessary for spontaneous recovery to occur, and to help in maintaining the very sick patient until an organ is available. Key to all of this and indeed dependent on it, is early recognition of the patients with ALF and their referral to a specialist liver centre where all the expertise and facilities, including liver transplantation, are available for treating what is still a rare disease but one if which poorly treated remains a killer.

Conflict of interest

William Bernal: Consulting fees for Vital Therapies Inc. and Ocera Therapeutics. William M Lee: Research support from Cumberland Pharmaceuticals and Ocera Therapeutics. Julia Wendon: None reported. Fin Stolze Larsen: None reported. Roger Williams: None reported.

References

[1] Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis 1970;3:282–298.
[2] Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013;369:2525–2534.
[3] Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–954.
[4] Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010;376:190–201.
[5] Acharya SK, Batra Y, Hazari S, Choudhury V, Panda SK, Dattagupta S. Etiopathogenesis of acute hepatic failure: Eastern versus Western countries. J Gastroenterol Hepatol 2002;17:S268–S273.
[6] Ostapowicz G, Lee WM. Acute hepatic failure: a Western perspective. J Gastroenterol Hepatol 2000;15:480–488.
[7] Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013;346:f403.
[8] O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet 1993;342:273–275.
[9] Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl 2008;14:S67–S79.
[10] Makin A, Wendon J, Williams R. A seven year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). Gastroenterology 1995;109:1907–1916.
[11] Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856–864.
[12] Karkhanis J, Verna EC, Chang MS, et al. Steroid use in acute liver failure. Hepatology 2014;59:612–621.
[13] Ichai P, Duclos-Vallee J-C, Guettier C, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007;13:996–1003.
[14] O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445.
[15] Khandelwal N, James LP, Sanders C, Larson AM, Lee WMand the Acute Liver Failure Study G. Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. Hepatology 2011;53:567–576.
[16] Ware A, D'agostino A, Combes B. Cerebral edema: a major complication of massive hepatic necrosis. Gastroenterology 1971;61:877–884.
[17] Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982;23:625–629.
[18] Bernal W, Hyyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 2013;59:74–80.
[19] Oketani M, Ido A, Nakayama N, et al. Etiology and prognosis of fulminant hepatitis and late-onset hepatic failure in Japan: summary of the annual nationwide survey between 2004 and 2009. Hepatol Res 2013;43:97–105.
[20] Trewby PN, Williams R. Pathophysiology of hypotension in patients with fulminant hepatic failure. Gut 1977;18:1021–1026.
[21] Larsen FS, Ejlersen E, Hansen BA, Knudsen GM, Tygstrup N, Secher NH. Functional loss of cerebral blood flow autoregulation in patients with fulminant hepatic failure. J Hepatol 1995;23:212–217.
[22] Bemeur C, Butterworth RF. Liver-brain proinflammatory signalling in acute liver failure: role in the pathogenesis of hepatic encephalopathy and brain edema. Metab Brain Dis 2013;28:145–150.
[23] Rama Rao KV, Jayakumar AR, Norenberg MD. Brain edema in acute liver failure: mechanisms and concepts. Metab Brain Dis 2014;29:927–936.
[24] Norenberg MD. Oxidative and nitrosative stress in ammonia neurotoxicity. Hepatology 2003;37:245–248.
[25] Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [H–C] nuclear magnetic resonance study. Hepatology 2003;37(2):420–428.
[26] Tofteng F, Larsen FS. Monitoring extracellular concentrations of lactate, glutamate, and glycerol by in vivo microdialysis in the brain during liver transplantation in acute liver failure. Liver Transpl 2002;8:302–305.
[27] Tandon BN, Joshi YK, Tandon M. Acute liver failure. Experience with 145 patients. J Clin Gastroenterol 1986;8:664–668.
[28] Karvellas CJ, Fix OK, Battenhouse H, et al. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med 2014;42:1157–1167.
[29] Jalan R, Damink SW, Deutz NE, Lee A, Hayes PC. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. Lancet 1999;354:1164–1168.
[30] Karvellas C, Stravitz R, Battenhouse H, Lee W, Schilsky M, ALFSG U. Therapeutic hypothermia in acute liver failure: a multi-center retrospective cohort analysis. Liver Transpl 2014;21:4–12.
[31] Larsen FS, Murphy N, Bernal W, et al. The prophylactic effect of mild hypothermia to prevent brain edema in patients with acute liver failure: results of a multicenter, randomized, controlled trial. J Hepatol 2011;54:S26.
[32] Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. J Cereb Blood Flow Metab 2004;24:798–804.
[33] Saliba F, Camus C, Durand F, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med 2013;159:522–531.
[34] Henrion J. Hypoxic hepatitis. Liver Int 2012;32:1039–1052.
[35] Stravitz RT, Lisman T, Luketic VA, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol 2012;56:129–136.
[36] Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004;39:464–470.
[37] Levy B, Perez P, Gibot S, Gerard A. Increased muscle-to-serum lactate gradient predicts progression towards septic shock in septic patients. Intensive Care Med 2010;36:1703–1709.
[38] Cholongitas E, O'Beirne J, Betrossian A, et al. Prognostic impact of lactate in acute liver failure. Liver Transpl 2008;14:121–122, author reply 3.
[39] Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 2002;359:558–563.
[40] Leithead JA, Ferguson JW, Bates CM, et al. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. Gut 2009;58:443–449.
[41] Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32:734–739.
[42] Miyake Y, Iwasaki Y, Terada R, Takaguchi K, Sakaguchi K, Shiratori Y. Systemic inflammatory response syndrome strongly affects the prognosis of patients with fulminant hepatitis B. J Gastroenterol 2007;42(6):485–492.
[43] Slack AJ, Auzinger G, Willars C, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int 2014;34:42–48.
[44] Audimoolam VK, McPhail MJ, Wendon JA, et al. Lung injury and its prognostic significance in acute liver failure. Crit Care Med 2014;42:592–600.
[45] Cote GA, Gottstein JH, Daud A, Blei ATAcute Liver Failure Study G. The role of etiology in the hyperamylasemia of acute liver failure. Am J Gastroenterol 2009;104:592–597.
[46] Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–517.
[47] Chiu A, Chan LM, Fan ST. Molecular adsorbent recirculating system treatment for patients with liver failure: the Hong Kong experience. Liver Int 2006;26:695–702.
[48] Demetriou AA, Brown Jr RS, Busuttil RW, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg 2004;239:660–667, discussion 7–70.
[49] Larsen FS, Schmidt LE, Wendon J, et al. Liver assisting with high-volume plasma exchange in patients with acute liver failure. Hepatology 2010;52:376A-A.
[50] Germani G, Theocharidou E, Adam R, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol 2012;57:288–296.
[51] Bernal W, Cross TJS, Auzinger G, et al. Outcome after wait-listing for emergency liver transplantation in acute liver failure: a single centre experience. J Hepatol 2009;50:306–313.
[52] O'Grady J. Timing and benefit of liver transplantation in acute liver failure. J Hepatol 2014;60:663–670.
[53] Rangnekar AS, Ellerbe C, Durkalski V, McGuire B, Lee WM, Fontana RJ. Quality of life is significantly impaired in long-term survivors of acute liver failure and particularly in acetaminophen-overdose patients. Liver Transpl 2013;19:991–1000.
[54] Macquillan GC, Seyam MS, Nightingale P, Neuberger JM, Murphy N. Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure. Liver Transpl 2005;11:1073–1079.
[55] Craig DGN, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther 2010;31:1064–1076.

Review

[56] McPhail MJW, Wendon JA, Bernal W. Meta-analysis of performance of King's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol 2010;53:492–499.

[57] Cholongitas E, Theocharidou E, Vasianopoulou P, et al. Comparison of the sequential organ failure assessment score with the King's College Hospital criteria and the model for end-stage liver disease score for the prognosis of acetaminophen-induced acute liver failure. Liver Transpl 2012;18:405–412.

[58] Cholongitas EB, Betrossian A, Leandro G, Shaw S, Patch D, Burroughs AK. King's criteria, APACHE II, and SOFA scores in acute liver failure. Hepatology 2006;43:881, author reply 2.

[59] Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364–1372.

[60] Perkins JD. Another formula to determine the prognosis of patients with acute liver failure. Liver Transpl 2009;15:986–991.

[61] Shakil AO, Jones BC, Lee RG, Federle MP, Fung JJ, Rakela J. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci 2000;45:334–339.

[62] Kumar R, Shalimar Sharma H, et al. Prospective derivation and validation of early dynamic model for predicting outcome in patients with acute liver failure. Gut 2012;61:1068–1075.

[63] Bernal W, Wang Y, Maggs J, et al. Personalised transplantation decision-making in acute liver failure; development and validation of a novel dynamic outcome prediction method for paracetamol-induced disease. J Hepatol 2014;60:S18.

[64] Wigg AJ, Gunson BK, Mutimer DJ. Outcomes following liver transplantation for seronegative acute liver failure: experience during a 12-year period with more than 100 patients. Liver Transpl 2005;11:27–34.