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.

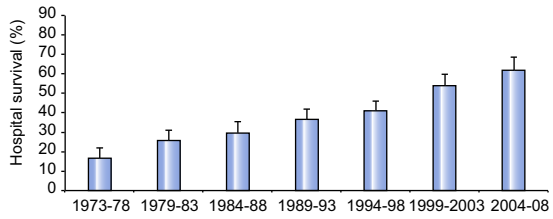

Fig. 1. Hospital survival for patients with ALF with encephalopathy of grade 3 and above, King's College Hospital, UK 1973–2008, (N = 2095). Error bars are 95% confidence intervals. p <0.0001. Source: Bernal *et al.* J Hepatol 2013; 59:74–80 [18].

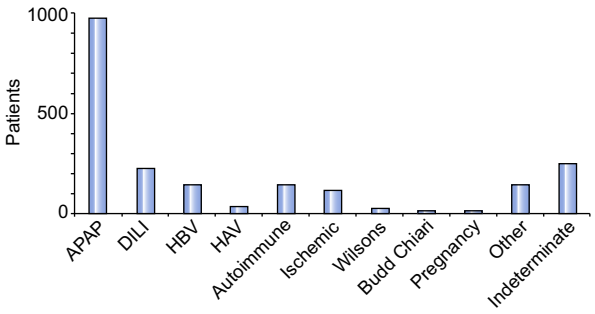

Fig. 2. Etiology of ALF in the USA: US ALFSG Adult Registry 1998–2014, (N = 2102). APAP, paracetamol; DILI, non-paracetamol drug-induced liver injury; HBV, Hepatitis B virus; HAV, Hepatitis A infection. Source: US ALFSG unpublished data October 2014.

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